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From: Davis, Minh-Tam
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For 103

1) Davis, T, 2000, Oncology (Williston Park, NY), 14(10): 1437, 1440-3.

2) Knox, S J, 1996, Clin Cancer Res: an official J of the Amer asssoc Cancer Res, 2(3): 457-70.

3) Davis, T, 1998, Proceed Amer Assoc Cancer Res Annual meeting, 39 p435.

4) Davis, T, 1997, Blood, V90, N10,1,1 (Nov 15): 2269 Page 507 A

5) Kaminski, MS, 1996, J clin oncology: Official j Amer Soc clin Oncology, 14(7): 1974-81.

6) Lazzarino, M, 1997, J Clin Oncology, 15(4): 1646-1653.

7) Kaminski, MS, 1994, Clin Res, 42(3): 405A.

Thank you.
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305-2008

11 (55%)/14 (53.8%)]. The major toxicities (grade 1<) of BAP were nausea/vomiting (34.7%), liver dysfunction (32.6%) and cardiac toxicity (15.2%). Onepatient died of ventricular tachycardia during CR, however, most of the toxicities were tolerable with sufficient clinical supportive care. These results indicated that BAP might have non-cross resistance to treatment which included Ara-C and DNP or IDR and might be included in the first line treatment of AML.

2267 326-IV

Intermittent intermediate dose ARA-C as consolidation therapy for AML in the elderly. W.R. Sperr, M. Piribauer, H. Agis, M. Mitterbauer, K. Geissler, O. Haas, C. Fonatsch, U. Jäger, I. Schwarzinger, F. Thalhammer, P. Valent and K. Lechner. *Dept. of Internal Med. I, Div. of Hematol. and Hemostaseol.; Clin. Inst. of Med. and Chem. Lab. Diagnostics; Inst. of Med. Biol.; Univ. of Vienna and St. Anna Kinderspital, Vienna, Austria.*

The incidence of acute myeloid leukemia (AML) increases with age and more than 50% of AML patients are aged 60 or more. Because of increased treatment-related toxicity the outcome for both, induction treatment and consolidation treatment in this patient group is poor. It has been shown, that intermittent high dose ARA-C is a highly effective consolidation treatment for AML, but not well tolerated in patients aged > 60. Therefore, in this study the efficacy and toxicity of intermittent intermediate dose ARA-C (IDAC; 2 x 1 g/m^2/day; days 1/3/5) was evaluated. 28 patients (MO: n = 4, M1: n = 4, M2: n = 6, M4: n = 4, M5: n = 6, M6: n = 2, M7: n = 1, acute MDS: n = 1, biphenotypic leukemia n = 1) aged > 60 years (median age: 68, range 63-89) received induction chemotherapy with daunorubicin, ARA-C and etoposide (DAV). 19 patients (65%) achieved complete remission (CR) after 1 (n = 17) or 2 (n = 2) cycles. From these patients 18 received up to 4 cycles of IDAC in 4 to 5 week intervals. The hematologic toxicity of the consolidation treatment was marked. The mean duration of neutropenia (ANC < 500) was 10.7 ± 3.4 days, the mean number of red cell and platelet concentrates was 3.1 ± 1.9 and 2.4 ± 1.3 units per cycle, respectively. However, the treatment was well tolerated. The mean number of days with fever (> 38° C) was 0.9 ± 1.4. The non-hematological toxicity was mild, no major hepatotoxicity or nephrotoxicity could be observed, no patient died during consolidation treatment. The disease free survival as well as the continuous complete remission at 12 months is 38% for all patients, 44% for patients with normal (n = 7) or favorable (n = 1) cytogenetics, the survival of responders 12 months 66%. Compared to previous treatment regimens IDAC seems to be at least equally effective but less toxic. Together, our data suggest, that intermittent intermediate dose ARA-C is an effective and well tolerated consolidation treatment for elderly patients.

2268 LYMPHOMA – IMMUNOTHERAPY, GENE THERAPY AND TARGETED THERAPY 327-IV

A multicenter phase II study of iodine-131 anti-B1 antibody (Bexxar) in patients (pts) with chemotherapy-relapsed/refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphoma (NHL). M.S. Kaminski, J. Vose, M. Saleh, A. Lister, S. Knox, D. Crowther, A.D. Zelenetz, D. Colcher and R. Wahl. *U of Michigan, Ann Arbor, MI; U of Nebraska, Omaha, NE; U of Alabama, Birmingham, AL; Stanford, Stanford, CA; Memorial Sloan-Kettering CC, NYC, NY; St. Bartholomew's Hospital, London; Christie Hospital, Manchester, UK.*

Forty-five pts with low-grade or transformed low-grade B-cell NHL were treated at 7 centers with Bexxar (Coulter Pharmaceutical), an iodine-131-labeled murine monoclonal antibody directed against the CD20 antigen on B cells. Pts received a single dosimetric dose (450 mg of unlabeled anti-B1 i.v. over 1 hour followed by 35 mg radiolabeled with 5 mCi I-131 over 1/2 hour) and then underwent periodic gamma camera scans and/or NaI probe counts over the next 7 days. Scan and/or probe data were used to calculate the required activity (mCi) of I-131 to deliver a desired therapeutic dose of radiation (cGy). This therapeutic dose was administered 7 to 14 days after the dosimetric dose and consisted of the same unlabeled and labeled antibody doses with the 35 mg dose labeled with enough I-131 to deliver a specified total body dose (a MTD determined in a prior phase I trial) of 65 cGy for pts with 100,000-149,999 platelets/mm3 and 75 cGy for pts with ≥150,000. Pts had been heavily pretreated with chemotherapy prior to study entry: median prior different regimens = 4 (range, 1-8). All had failed an anthracyline or anthracenedione-containing regimen and had relapsed within 1 year after completion of their last chemotherapy regimen (as per protocol). Other characteristics included: mean age = 51, histology (low-grade 76%, transformed 24%), bulky disease 42%. 36 pts received 75 cGy and 9 received 65 cGy total body dose; mean activity = 88 mCi (range, 45-177). Twenty-seven of 45 (60%) pts responded (PR + CR) and 12/45 (27%) had a complete response (CR). The median duration of CR has not been reached (range, 4.5-13.6+ months) with a median follow-up of 10 months and 8/12 pts have ongoing CRs. Seven of 11 (64%) pts with transformed NHL responded and 5/11 (45%) had a CR. Twelve of 19 (63%) pts with bulky disease responded (13% CR). The principal toxicity was hematologic; ANC < 100/mm3 = 4%, platelet count <10,000/mm3 = 11%. The nadir typically occurred at week 5-6 with recovery by week 8-9. Transient mild to moderate non-hematologic toxicity was also observed with the most frequent events being fatigue, nausea and fever. None of the 45 pts developed HAMA. These results in patients with poor prognostic factors indicate Bexxar to be a promising new agent for the treatment of low-grade and transformed low-grade NHL.

2269 328-IV

Retreatments with RITUXAN™ (Rituximab, Idec-C2B8) have significant efficacy, do not cause hama, and are a viable minimally toxic alternative in relapsed or refractory non-Hodgkin's lymphoma (NHL). T. Davis, R. Levy, C.A. White, D.G. Maloney, B. Link, W.S. Velasquez, C. Varns, C. Gardner and A.J. Grillo-López. *Stanford University, Stanford, CA; IDEC Pharmaceuticals Corp., San Diego, CA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Iowa, Iowa City, IA; St. Louis University Medical Center, St. Louis, MO.*

RITUXAN™, a chimeric anti-CD20 monoclonal antibody with murine variable regions and human IgG kappa constant regions, binds complement, mediates complement-dependent and antibody-dependent cellular cytotoxicity and can directly induce apoptosis *in vitro*. Integrated analysis of 166 relapsed or refractory low-grade or follicular NHL patients on the pivotal trial and 37 similar patients on a Phase II trial treated with 375 mg/m^2 IV q week x 4 doses, revealed an overall response rate of 50% in evaluable patients (48% intent-to-treat). Integrated safety analysis of 315 patients treated on multiple single agent RITUXAN trials performed in patients with relapsed or refractory low-grade or follicular NHL revealed that most adverse events were reversible and infusion-related, resolving completely in less than a few hours. Currently we report on an interim analysis of a Phase II multicenter study to evaluate the safety and efficacy of RITUXAN retreatment in patients with relapsed low-grade or follicular B-cell NHL who have previously responded to RITUXAN 375 mg/m^2 weekly x 4. Characteristics of the 31 patients included: 52% female; median age 51 years; median time from diagnosis: 4.3 years; 80% WHO PS 0-1; 1-4 prior chemotherapy regimens, with 10% having relapsed post-ABMT. 29% had ≥2 extranodal sites. Investigators reported responses in 10 of 25 patients (40%), including one patient who had responded to both a 2nd and 3rd course of treatment, median duration of response has not been reached at 5.5+ months and median time to progression in responders had not been reached at a median of 7.0+ months. Safety analysis of 29 patients for whom full safety data was available revealed that most adverse events were reversible and infusion-related, similar to those seen with primary infusions. Grade 3 or 4 treatment-related adverse events occurring between study entry and 30 days following the last dose included only a single patient with leukopenia. Although the overall incidence of HACA in 315 patients treated with single agent RITUXAN has been <1% (3/315), 2 of these 3 patients were in the retreatment group. One patient was retreated despite detectable though not quantifiable serum HACA. This patient developed no unusual adverse events and achieved near complete remission upon retreatment. A second patient was found to have detectable HACA 7 months post-retreatment after achieving a PR. Retreatment with RITUXAN (Rituximab) is not associated with an increase in adverse events and has efficacy permitting an additional period of time without antineoplastic treatment in patients with relapsed or refractory low-grade or follicular NHL who have previously responded to RITUXAN.

2270 329-IV

A comparison of toxicity and stimulated immune responses from adjuvants used in idiotype vaccination of B cell lymphoma. T.A. Davis, F.J. Hsu, C.B. Caspar, T.M. Liles, D. Czerwinski, B. Taidi and R. Levy *Stanford University, Stanford, Ca., 94305.*

Idiotype vaccination post chemotherapy in patients with advanced stage B cell non-Hodgkins lymphoma (NHL) can stimulate both humoral and cellular tumor specific immune responses (IR) which correlate with prolonged freedom from disease progression and overall survival (Blood, 89: 3129-35, 1997). In a series of clinical trials for patients with low and intermediate grade B cell NHL, we have evaluated vaccines containing tumor specific idiotype coupled to the carrier protein KLH in different adjuvants; Syntex Adjuvant Formulation (SAF1), "incomplete" SAF (ISAF) which does not contain Thr-MDP (a mycobacterial protein) and QS-21 (a saponin from tree bark). At least 2 months after cytoreduction to maximal response using standard chemotherapies or ABMT, patients received five vaccinations over a period of five months. The vaccines cantained 0.5 mg of idiotype protein coupled to 0.5 mg of KLH in adjuvant and were given in two SQ injections. Testing for humoral and cellular immune responses were performed throughout the vaccination period and 1 month after the last vaccination. 9 patients received only ISAF, 65 received SAF1 in at least their first vaccination and 8 patients have completed vaccination with QS-21. Vaccinations containing SAF1 frequently stimulated significant local skin reactions, arthralgias, myalgias, fever and transient transaminase elevations in one case. 8% of patients were unable to tolerate SAF1 and were switched to ISAF for the completion of their vaccinations. ISAF and QS-21 displayed similar but much less severe toxicities, stimulating only minimally irritating local reactions and mild systemic symptoms which did not prevent completion of the vaccine course. All vaccinated patients mounted robust immune responses to KLH and 98% had both humoral and cellular responses. Percentages of patients mounting idiotype specific immune responses are as follows:

% of patients with detectable IR				
	humoral	cellular	total	Patients with NED
ISAF	44	33	67	71
SAF1	33	8	35	60
QS-21	50	38	75	100

NED - percentage of patients with-no clinically detectable disease prior to vaccination who subsequently developed idiotype specific immune responses.

While the number of evaluable patients treated with QS-21 is small, our preliminary experience suggests that QS-21 stimulates IR in a higher percentage of patients than the other adjuvants, with an increased frequency of cellular responses. Patients with no detectable residual disease are more likely to make an IR. QS-21 is easily tolerated and is a potent stimulator of both humoral and cellular IR to idiotype protein in patients with NHL.

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RAPID PUBLICATION

Iodine-131–Anti-B1 Radioimmunotherapy for B-Cell Lymphoma

By Mark S. Kaminski, Kenneth R. Zasadny, Isaac R. Francis, Melissa C. Fenner, Charles W. Ross, Adam W. Milik, Judith Estes, Melissa Tuck, Denise Regan, Susan Fisher, Stephan D. Glenn, and Richard L. Wahl

Purpose: **The CD20 B-lymphocyte surface antigen expressed by B-cell lymphomas is an attractive target for radioimmunotherapy, treatment using radiolabeled antibodies. We conducted a phase I dose-escalation trial to assess the toxicity, tumor targeting, and efficacy of nonmyeloablative doses of an anti-CD20 monoclonal antibody (anti-B1) labeled with iodine-131 (^{131}I) in 34 patients with B-cell lymphoma who had failed chemotherapy.**

Patients and Methods: **Patients were first given trace-labeled doses of ^{131}I-labeled anti-B1 (15 to 20 mg, 5 mCi) to assess radiolabeled antibody biodistribution, and then a radioimmunotherapeutic dose (15 to 20 mg) labeled with a quantity of ^{131}I that would deliver a specified centigray dose of whole-body radiation predicted by the tracer dose. Whole-body radiation doses were escalated from 25 to 85 cGy in sequential groups of patients in 10-cGy increments. To evaluate if radiolabeled antibody biodistribution could be optimized, initial patients were given one or two additional tracer doses on successive weeks, each dose preceded by an infusion of 135 mg of unlabeled anti-B1 one week and 685 mg the next. The unlabeled antibody dose resulting in the most optimal tracer biodistribution was also given before the radioimmunotherapeutic dose. Later patients were given a single tracer dose and radioimmunotherapeutic dose preceded by infusion of 685 mg of unlabeled anti-B1.**

Results: **Treatment was well tolerated. Hematologic toxicity was dose-limiting, and 75 cGy was established as the maximally tolerated whole-body radiation dose. Twenty-eight patients received radioimmunotherapeutic doses of 34 to 161 mCi, resulting in complete remission in 14 patients and a partial response in eight. All 13 patients with low-grade lymphoma responded, and 10 achieved a complete remission. Six of eight patients with transformed lymphoma responded. Thirteen of 19 patients whose disease was resistant to their last course of chemotherapy and all patients with chemotherapy-sensitive disease responded. The median duration of complete remission exceeds 16.5 months. Six patients remain in complete remission 16 to 31 months after treatment.**

Conclusion: **Nonmyeloablative radioimmunotherapy with ^{131}I-anti-B1 is associated with a high rate of durable remissions in patients with B-cell lymphoma refractory to chemotherapy.**

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NEW THERAPEUTIC options are needed for patients with non-Hodgkin's lymphoma. Recent studies have indicated that only approximately 50% of patients with advanced intermediate- and high-grade lymphoma can expect to be cured using conventional chemotherapy for primary treatment, and high-dose chemotherapy (or chemoradiotherapy) with bone marrow transplantation or second-line chemotherapy regimens for refractory or relapsed disease.[1,2] In addition, while patients with low-grade lymphoma can often achieve an initial remission with chemotherapy, virtually all patients inevitably relapse. Reinduction and maintenance of remission becomes more difficult with each recurrence as the disease becomes more resistant to chemotherapy and/or transforms to an intermediate- or high-grade histology.[3,4] Eventually patients die from disease or complications of treatment.

Radioimmunotherapy is currently under investigation as a new approach to the treatment of this disease. In this form of treatment, radionuclide-labeled monoclonal antibodies recognizing tumor-associated antigens are administered systemically to selectively target radioactivity to tumor cells. If isotopes emitting beta particles are used for antibody labeling, the radiation emitted from a radiolabeled antibody bound to a tumor cell also kills neighboring cells because the path length of beta particles can extend over several cell diameters. This crossfire of beta particles can thus destroy antigen-positive and -negative tumor cells, as well as untargeted antigen-positive tumor cells within a tumor. This feature distinguishes radioimmunotherapy from approaches in which toxins are conjugated to antibodies (immunotoxins), the latter requiring targeting of all tumor cells and also internalization of the toxin by all cells to accomplish complete eradication of

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disease. In addition, the antibodies carrying the radioisotope may recruit cytolytic host immune mechanisms or may directly affect tumor-cell proliferation.

In a previous report,[5] we described preliminary results obtained in the first ten patients entered onto a then ongoing phase I dose-escalation trial evaluating nonmyeloablative doses of iodine-131 (^{131}I)-labeled anti-B1 antibody, a mouse monoclonal antibody directed against the CD20 B-lymphocyte surface antigen expressed by nearly all B-cell lymphomas.[6] In the present report, we describe the findings of the completed phase I trial in 34 patients with extended follow-up. The results of this trial indicate that a single dose of nonmyeloablative ^{131}I-anti-B1 radioimmunotherapy is capable of inducing durable clinical remissions with minimal or modest toxicity in a high proportion of patients in whom multiple chemotherapy regimens have failed.

PATIENTS AND METHODS

Selection of Patients

Patients eligible for this study were adults with non-Hodgkin's B-cell lymphoma expressing the CD20 antigen who had failed at least one prior chemotherapy regimen and who had assessable and measurable disease; less than 25% of the intertrabecular marrow space involved by lymphoma cells in bilateral iliac crest bone marrow biopsies; no other treatment for at least 4 weeks before entry; an absolute granulocyte count greater than 1,500/μL; a platelet count greater than 100,000/μL; normal hepatic and renal function; no other serious coexistent illnesses; Karnofsky performance score of at least 60; life expectancy of at least 3 months; and no serum human anti-mouse antibodies (HAMA). All patients gave written informed consent to their participation in the study, which was approved by the institutional review board of the University of Michigan.

Preparation and Iodination of the Anti-B1 Antibody

The anti-B1 mouse immunoglobulin (Ig)G2a monoclonal antibody was provided by Coulter Corporation, Miami, FL. Radioiodination of the antibody with ^{131}I, purification of the radiolabeled product, verification of its immunoreactivity, and testing for its contamination by pyrogens was performed as previously described.[5,7,8]

Tracer Dose and Dosimetry Studies

Because of potential differences in radiolabeled antibody pharmacokinetics among patients, the radiation dose to the whole body, tumors, and normal organs delivered by a small dose of radiolabeled anti-B1 was determined before administering a larger therapeutic dose to individual patients. All patients were hospitalized and received 15 to 20 mg of anti-B1 antibody trace-labeled with approximately 5 mCi of ^{131}I over 30 minutes. Serial quantitative gamma-camera scans, as well as whole-body radioactivity counts recorded by a sodium iodide scintillation probe, were obtained beginning 1 hour after tracer dose administration and then daily for at least 5 days. Dosimetric estimates were then made according to methods previously described.[5,9,10-14]

To evaluate if preinfusing unlabeled antibody could optimize radiolabeled antibody tumor targeting, one or two additional tracer doses were given on successive weeks, each of which was immediately preceded by a 60-minute infusion of 135 mg of unlabeled anti-B1 one week and 685 mg the next week. Patients who were entered later in the trial received only one tracer dose preceded by a 685-mg unlabeled antibody after a 685-mg dose appeared to be optimal.

Diphenhydramine (50 mg) and acetaminophen (650 mg) were given orally as premedication before each infusion. Saturated potassium iodide was given orally (two drops three times daily) beginning the day before the first antibody infusion for at least 14 days to inhibit uptake of radioactive iodine by the thyroid.

Radioimmunotherapeutic Dose

At least 1 week after the last tracer dose, 15 to 20 mg of anti-B1 labeled with a higher amount of radioactivity—the radioimmunotherapeutic dose—was administered. This dose was preceded by the infusion of the unlabeled antibody dose that produced the highest ratio of tumor radiation dose to whole-body radiation dose in a patient's tracer studies. The radioactivity (in millicuries) of the radioimmunotherapeutic dose was individualized so that a patient would receive a specified dose (in centigrays) of whole-body radiation predicted by the tracer doses. Patients were again premedicated with diphenhydramine and acetaminophen, and potassium iodide was given for 14 days. In addition, potassium perchlorate (200 mg three times daily) was given for 7 days beginning the day of the infusion. Patients were isolated in lead-shielded rooms until their whole-body radioactivity was less than 5 mrem/hr at 1 meter.

Patients were considered for re-treatment 12 weeks after the first dose if they had achieved less than a complete remission. Re-treatment consisted of a tracer dose followed 1 week later by a radioimmunotherapeutic dose that was adjusted to deliver the same whole-body radiation dose given previously. Usually, the same dose of unlabeled antibody used for the first radioimmunotherapeutic dose was infused before the re-treatment tracer and therapeutic doses.

A complete remission was defined as a complete disappearance of all detectable disease for at least 1 month or lack of change of a minimal, residual radiographic abnormality for at least 6 months. A partial response was defined as a reduction of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 1 month. Complete reevaluation of disease status (including physical examination; computed tomography [CT] scan of the chest, abdomen, and pelvis; bone marrow biopsies if positive for lymphoma at last evaluation; blood counts and chemistries) was performed 4 to 6 weeks and 12 weeks after therapy, and then every 3 months thereafter.

Evaluation of Toxicity

Toxicity was scored according to the National Cancer Institute common toxicity criteria. Groups of at least three patients received escalating whole-body radiation doses, starting at 25 cGy and increasing by 10-cGy increments until a maximally tolerated dose not requiring support by bone marrow transplantation was determined. This dose level was defined as one whole-body dose level below that at which no more than two of three patients experienced grade 3 or 4 toxicity and at which no more than one of six patients experienced such toxicities. Dose-limiting hematologic toxicity was defined as any grade 3 toxicity lasting more than 14 days and any grade 4 toxicity lasting more than 7 days. Complete blood cell and platelet counts were obtained weekly for at least 6 weeks. When grade 1 toxicity was observed, twice weekly blood counts were obtained until counts had recovered and stabilized. Hematopoietic

growth factors, RBC transfusions, or platelet transfusions were not to be given unless patients developed febrile neutropenia and/or obvious signs of bleeding. Hepatic enzyme, renal function, and electrolyte studies were performed 2, 6, and 12 weeks after radioimmunotherapy, and then every 3 months. Serum thyrotropin was measured every 3 months after radioimmunotherapy.

Peripheral-blood B and T cells were quantitated by flow cytometry as previously described[5] at study entry, 6 and 12 weeks after the radioimmunotherapeutic dose, and then every 3 months until the number of B cells returned to normal levels. Serum immunoglobulin concentrations were measured each time flow cytometry studies were performed.

Serum was tested for HAMA before each tracer and radioimmunotherapeutic dose and then 2, 6, and 12 weeks after a radioimmunotherapeutic dose. An enzyme-linked immunosorbent assay was used as described previously,[9] as well as a commercial test kit (Immunostrip; Immunomedics, Newark, NJ).

RESULTS

Tracer Dose and Dosimetry Studies

The clinical characteristics of the 34 patients who were entered onto the study are listed in Table 1. All patients were given at least one tracer infusion of ^{131}I-anti-B1. Twenty-three patients received additional tracer doses in succeeding weeks that were preceded by infusions of different amounts of unlabeled anti-B1 to determine if preinfusion of unlabeled antibody could more optimally distribute subsequently administered radiolabeled antibody (Table 2). This was based on the premise that unlabeled antibody may preblock nonspecific binding sites and normal B-cell antigen sinks (such as the spleen), thus allowing greater access of radiolabeled antibody to tumor sites. Although a detailed account of the results of these tracer studies will be published elsewhere, dosimetric and clinical observations suggested that in some cases, unlabeled infusions (especially those containing higher protein doses) could improve tumor targeting and contribute to tumor responses. Thus, tracer doses without a preceding unlabeled antibody infusion were discontinued and eventually only one tracer dose, preceded by a 685-mg unlabeled antibody infusion, was given in the last nine patients (Table 2).

Definite tumor imaging was observed in all patients with tumor sites larger than 2 cm. On average, tracer studies indicated that tumors received approximately 17 times the radiation dose delivered to the whole body.

Radioimmunotherapeutic Infusions

Twenty-eight patients were given a radioimmunotherapeutic infusion. Of the six patients who were not, three developed HAMA and three had severe physiologic deterioration from rapid progression of disease during tracer studies. One patient who developed HAMA after tracer infusions was given a radioimmunotherapeutic infusion as an exception to the protocol. Most patients (71%) were preinfused with 685 mg of unlabeled anti-B1 before the radioimmunotherapeutic infusion (Table 2). Patients generally could be released from radiation isolation within 3 days after the infusion. Radioimmunotherapeutic infusions delivered 25 to 85 cGy to the whole body and a mean (± SE) maximal dose to any of a patient's tumors of 925 ± 150 cGy (range, 141 to 2,584 cGy).

Table 1. Characteristics of 34 Patients with B-Cell Lymphoma Treated with ^{131}I-Anti-B1 Antibody

Characteristic	No.	%
Median age (yr)	52	
Range	27-74	
Male sex	22	65
Tumor histology*		
Low grade	17	50
Transformed	8	23.5
De novo intermediate grade	9	26.5
Mean prior chemotherapy regimens	3.1	
Range	1-8	
Disease resistant to last chemotherapy regimen	21	62
Tumor burden > 500 g†	14	41
Bone marrow involvement‡	9	26

*Among the patients with low-grade histologies, 7 had follicular small cleaved-cell lymphoma, 7 had follicular mixed small cleaved-cell and large-cell lymphoma, 2 had follicular and diffuse mixed small cleaved-cell and large-cell lymphoma, and 1 had small-cell plasmacytoid lymphoma. Among the patients with transformed histologies, 4 had converted from follicular small cleaved-cell lymphoma to diffuse large-cell lymphoma, 1 had converted from follicular mixed small cleaved-cell and large-cell lymphoma to follicular large-cell lymphoma, 2 had converted from follicular and diffuse mixed small cleaved-cell and large-cell lymphoma to diffuse large-cell lymphoma, and 1 had converted from follicular small cleaved-cell lymphoma to immunoblastic lymphoma. Among the patients with de novo intermediate grade histologies, 5 had diffuse large-cell lymphoma, 1 had diffuse mixed small- and large-cell lymphoma, 1 had anaplastic large-cell lymphoma, 1 had follicular large-cell lymphoma, and 1 had diffuse mantle-cell lymphoma.

†Using the 10-mm thick axial slices used for diagnostic CT scanning, tumor boundaries were traced using an electronic cursor. Volumes of the tumor were then automatically derived by the computer. Total tumor volume was determined by summing tumor volumes from all slices in which tumor was outlined. This sum was then divided by 100 to obtain total tumor mass in grams.

‡All patients whose bone marrow was involved had < 25% of the intertrabecular marrow space occupied by lymphoma, as per protocol eligibility criteria.

Toxicity

Unlabeled and radiolabeled-antibody infusions were usually accompanied by few or no side effects. Nonhematologic toxicities were generally mild (grade 1 and 2), with low-grade fever being most common (Table 3). Mild fatigue and nausea tended to be more frequent with radio-

Table 2. Quantities of Unlabeled Anti-B1 Given Just Before Tracer and Radioimmunotherapeutic Doses

	No. of Patients
Tracer dose* (mg)	
0	2
0 and 135	10
0, 135, and 685	8
135 and 685	5
685	9
Radioimmunotherapeutic dose† (mg)	
0	3
135	5
685	20

*When more than 1 dose of unlabeled antibody is indicated, the doses were given at least 1 week apart. In addition, only tracer doses preceding the first radioimmunotherapeutic dose are included.

†Only the first radioimmunotherapeutic dose is included.

immunotherapeutic doses than tracer doses, especially in patients given the higher radioimmunotherapeutic doses. Only one grade 3 event occurred during a tracer infusion (postural hypotension treated with a brief course of intravenous fluids and vasopressors) in a patient who was subsequently found to have developed HAMA during tracer studies. Among five patients who developed urticaria were three who had lymphoma involving the skin. In these three patients, erythema and urticaria developed solely at cutaneous tumor sites during the infusion of unlabeled anti-B1. In one case, this led to nearly complete regression of skin lesions within 1 week of receiving a tracer dose.

The dose-limiting toxicity was hematologic. After two of three patients given a whole-body dose of 85 cGy experienced dose-limiting grade 3 and 4 leukopenia and thrombocytopenia, the maximally tolerated whole-body radiation dose was determined to be 75 cGy for patients who had not undergone autologous bone marrow transplantation. Patients given 75 cGy usually had only mild to moderate myelosuppression 4 to 6 weeks after treatment. Three posttransplant patients were treated in this trial and appeared more susceptible to myelosuppression. Because one patient given 55 cGy and another given 65 cGy experienced dose-limiting grade 3 and 4 toxicity, a separate phase I study for posttransplant patients is in progress in which lower whole-body doses are being tested.

Complete or near-complete depletion of CD19- and CD20-positive B cells from the peripheral blood was observed in all patients after radioimmunotherapy. Recovery was observed in all patients after 3 months (except one patient in whom recovery took 6 months). No changes in serum Ig concentrations and no opportunistic infections were observed during this recovery period. Only four patients developed HAMA during tracer studies, and two after radioimmunotherapeutic doses. No hypothyroidism has been observed in any patients to date.

One patient developed a myelodysplastic syndrome followed by acute myelocytic leukemia in long-term follow-up. Because the patient had no significant myelosuppression with his radioimmunotherapy, had the onset of myelodysplasia within 6 months of protocol entry, and had been exposed to chemotherapy (including alkylating agents) 15 and 5 years before radioimmunotherapy, the direct involvement of radioimmunotherapy in the etiology of this hematologic disorder is unlikely, but cannot be entirely excluded.

Tumor Responses

Of the 28 patients given a radioimmunotherapeutic dose, 22 (79%) achieved either a complete or partial response. Fourteen (50%) achieved a complete remission. Responses were achieved at all whole-body dose levels. Six patients were given a second radioimmunotherapeutic dose after achieving a partial or minor response after the first dose. A further response was observed in three of these latter patients, but none achieved a complete remission. Ten patients achieved minor or partial responses during tracer studies, including two with partial responses who did not receive a radioimmunotherapeutic dose because they had developed HAMA. Eight of these 10 patients responded only after receiving a tracer dose that was preceded by a 685-mg unlabeled antibody infusion.

Table 3. Nonhematologic Toxicities of Tracer Doses and Radioimmunotherapeutic Doses of ^{131}I-Anti-B1 in 34 Patients

Side Effect*	No. of Patients	% of Tracer Doses†	% of Radioimmunotherapeutic Doses‡	% of All Infusions§
Fever	14	29	34	31
Chills/rigors	11	8	26	14
Fatique	7	0	18	6
Nausea	6	4	16	8
Urticaria	5	8	5	7
Pruritis	2	5	5	5
Emesis	3	3	8	4
Arthralgia/myalgia	2	0	5	2
Hypotension	1	1	0	<1
Rash	1	1	3	2
Facial flushing	2	1	3	2

*All side effects were grade 1 or 2 in severity except for grade 3 hypotension in 1 patient. This grade 3 event occurred in a patient who was subsequently found to have developed HAMA during tracer studies. Hypotension was rapidly reversed with intravenous fluids and vasopressors.

†Based on a total of 76 infusions.

‡Based on a total of 38 infusions.

§Based on a total of 114 infusions.

Table 4. Tumor Responses of 28 Patients Given a Radioimmunotherapeutic Dose of ^{131}I-Anti-B1 According to Histology and Resistance to Chemotherapy*

	Low Grade		Transformed		De Novo Intermediate Grade	
	CR	CS	CR	CS	CR	CS
Total	8	5	5	3	6	1
Complete remission	5	5	2	1	0	1
Partial response	3	0	1	2	2	0
% response	100	100	60	100	33	100

Abbreviations: CR, chemotherapy resistant; CS, chemotherapy sensitive.
*Resistance to chemotherapy is defined herein as a response lasting for < 1 month after the last chemotherapy treatment received by the patient.

In general, tumor responses appeared to be more rapid after the radioimmunotherapeutic dose in patients who had some response to tracer doses. For patients who responded to radioimmunotherapeutic doses, tumor regression was greatest within the first month after receiving the dose, but in some patients, tumors continued to regress for several months.

Tumor responses according to tumor histology and resistance to chemotherapy are listed in Table 4 for the patients given radioimmunotherapeutic doses. All 13 patients who had low-grade lymphoma responded, and 10 achieved a complete remission. Six of eight patients with transformed lymphoma responded, and three achieved a complete remission. Of the seven patients with de novo intermediate-grade lymphoma, three responded and one achieved a complete remission. Thirteen of 19 patients (68%) whose disease was resistant to their last course of chemotherapy (a response lasting for < 1 month after treatment) and all patients with chemotherapy-sensitive disease responded.

Twenty-five of 28 patients given radioimmunotherapeutic doses had disease that was resistant to at least one chemotherapy regimen (mean, 2.1 regimens; range, 1 to 5) at any point in the history of their illness. Of 11 patients whose disease was resistant to doxorubicin-containing regimens, eight responded to anti-B1 radioimmunotherapy. Similarly, six of seven patients with disease resistant to cisplatin-containing regimens and three of four patients with disease resistant to the purine analog fludarabine responded. Two of three patients who had relapsed after autologous bone marrow transplantation achieved complete remissions. Responses to anti-B1 radioimmunotherapy were longer than those to any previous courses of chemotherapy in 11 patients.

Complete remissions were achieved in patients with a range of tumor burdens (Table 5), including five of nine patients with very large burdens (> 500 g). Tumor burdens were quantitated radiographically using CT technology as described in the footnote to Table 1.

The median duration of all complete remissions exceeded 16.5 months at last evaluation. Of 14 patients who achieved a complete remission, six remain in remission without further treatment (Table 5). Relapses occurred solely in areas that were not involved by tumor at the time of study entry in six of eight cases, and were confirmed by biopsy in five patients. In all five patients, the tumor tissue still expressed the CD20 target antigen. Four of these patients were re-treated and responded to the same whole-body dose given for their initial radioimmunotherapy. Two had a partial response that lasted 2 and 7 months, respectively, and two remain in complete remission 4 and 14 months after re-treatment, respectively.

Eighteen of 28 patients given radioimmunotherapeutic doses were alive after a median follow-up duration of 21 months. All six patients who did not respond to treatment died of disease, in contrast to only three of 22 responding patients. One responding patient died of myelodysplastic syndrome and acute myelocytic leukemia.

Table 5. Treatment Characteristics of Patients Who Had Complete Remissions After ^{131}I-Anti-B1 Radioimmunotherapy

Patient No.	Whole-Body Dose (cGy)	^{131}I Dose (mCi)	Hematologic Toxicity (grade)	Tumor Burden (grams)	Duration of Remission* (months)
4	25	57	1	> 500	8
	25	37	2		
6	35	40	1	60	16
8	45	40	2	< 50	13
10	45	40	None	200	13
13	45	41	None	122	12
15	55	44	3	106	31+
16	55	71	2	> 500	14
20	65	56	3	93	28+
22	65	93	3	> 500	18
25	75	153	None	> 500	22+
26	75	67	3	< 50	19+
27	85	98	None	92	10
30	65	62	3	90	17+
34	75	103	2	> 500	16+

*Plus sign denotes that the patient was still in complete remission at the time indicated.

DISCUSSION

The data from this completed phase I trial strongly suggest that a single, well-tolerated radioimmunotherapeutic dose of ^{131}I-anti-B1 results in a high response rate in patients with B-cell lymphoma. Indeed, when all 34 patients in this trial were included on an intention-to-treat basis, the response rate was 71%. The response rate in the patients who actually received a radioimmunotherapeutic dose was 79%, and 64% of those responses were complete. Furthermore, the complete responses were durable (exceeding a median of 16.5 months), and almost half of them (six of 14) continue without disease recurrence after 16 to 31 months. In addition, we have shown that it is possible to reinduce remissions in patients once they have relapsed.

Notably, these results were achieved in a group of patients with a poor prognosis. These patients had already experienced failure of an average of 3.1 different chemotherapy regimens (range, 1 to 8) that included the most active drugs for lymphoma. Anthracyclines, for instance, were part of the drug regimens in 91% of the patients. More importantly, 89% of the patients given a radioimmunotherapeutic dose had disease that was resistant to at least one of all of these chemotherapy regimens, and 68% had disease that was resistant to the last chemotherapy regimen they received. Despite this, 68% of the latter patients responded to ^{131}I-anti-B1 radioimmunotherapy. In addition, the median duration of response to the last chemotherapy regimen for all patients was less than 1 month compared with more than 11 months after radioimmunotherapy. And almost 40% of patients (11 of 28) had a longer response to ^{131}I-anti-B1 radioimmunotherapy than to any previous course of chemotherapy. These data indicate that the antitumor mechanisms of ^{131}I-anti-B1 are highly independent of those of most chemotherapeutic agents and thus suited to the treatment of patients failing primary chemotherapy.

The finding that five of nine patients with massive tumor burdens (> 500 g) achieved a durable complete remission with a single treatment suggests the cytoreductive potential of this therapy. Additionally, in none of three patients who relapsed did the disease recur in a previous bulky site of disease, possibly indicating long-term sterilization of bulky sites. This also suggests that this treatment need not be restricted to patients with smaller tumor burdens.

Patients with low-grade lymphoma were particularly responsive to this treatment. Indeed, 100% of these patients (13 of 13) responded, and 77% achieved a complete remission. Patients with transformed lymphoma (a particularly poor-prognostic group of low-grade lymphoma patients[3,15,16] also frequently responded (six of eight patients). Because some of our patients with low-grade lymphoma did not undergo a repeat tumor biopsy just before study entry, some of these patients may have had transformed lymphoma; therefore, the response rate for patients with transformed lymphoma may be underestimated. Although patients with de novo intermediate-grade lymphoma appeared to be less responsive, more patients will need to be studied to determine if there are inherent biologic differences in responsiveness to this treatment among the different histologic subtypes of B-cell lymphoma.

The frequency, quality, and duration of disease responses presented here appear to surpass those of other published studies using nonmyeloablative doses of different radiolabeled antibodies for B-cell lymphoma.[9,17-22] They can also be compared with those obtained by Press et al[23,24] from Seattle, who used myeloablative doses of ^{131}I-anti-B1. On average, the Seattle group used radioimmunotherapeutic radioactivity doses seven times those we used, thus requiring autologous bone marrow transplant support. As expected, these higher doses resulted in a substantially different and more severe toxicity profile, prolonged isolation to limit public radiation exposure, and hospitalization for the supportive management of severe myelosuppression and infections. Although the overall response rate (93%) and complete response rate (79%) in the Seattle study appears to be higher than ours, many patients were excluded from receiving radioimmunotherapeutic doses because they had high tumor burdens and did not fulfill strict antibody biodistribution criteria. Such patients were included in our study. In addition, a much higher proportion of patients treated in the Seattle series had low-grade lymphoma. Indeed, this was the group in which we had a 100% response rate. Thus, further studies will be needed to assess the costs, risks, and benefits associated with these two approaches to ^{131}I-anti-B1 radioimmunotherapy.

Such studies are particularly relevant, especially when one considers that our nonmyeloablative approach can probably be further streamlined by omitting the hospitalization of patients for tracer dosimetry studies and reducing such studies to only periodic whole-body probe or gamma camera counts, and by only hospitalizing patients for 2 to 3 days to fulfill radiation isolation requirements after the administration of the radioimmunotherapeutic dose. In this way, this treatment could be given by virtually all medical centers that already administer radioisotopes for therapeutic purposes.

A variety of antitumor mechanisms can be proposed for anti-B1 radioimmunotherapy: antibody-targeted radia-

tion, low-dose rate irradiation, whole-body irradiation, immune-mediated antibody effects, and direct antiproliferative antibody effects. It is likely that all of these mechanisms play some role, but their relative contributions are not clear. We favor antibody-targeted radiation to be the dominant mechanism because of the consistently rapid response observed after a radioimmunotherapeutic dose (within several days), the completeness of responses beyond that expected of unlabeled antibodies, and the apparent predominance of relapse in new rather than previous sites of disease (which one would not expect if the mechanism were totally based on nonspecific whole-body irradiation). However, the observation of responses to tracer doses indicates that unlabeled antibody effects may contribute to tumor responses in some cases. The local inflammatory and urticarial reactions observed in skin tumors during unlabeled antibody infusions and the preponderance of tumor responses in patients given the highest unlabeled antibody dose support this role of anti-B1. These unlabeled antibody effects may be mediated by anti-B1 recruitment of immune effectors[25,26] and/or antiproliferative signals mediated directly via CD20 binding.[27,28]

In light of these results, a multicenter phase II/III study in patients with chemotherapy-refractory B-cell lymphoma is planned. The possible use of radiolabeled anti-B1 as initial treatment for patients with advanced low-grade lymphoma is also being explored.

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PLATELET FACTOR 4 (PF4) IMPAIRS TISSUE FACTOR (TF)-MEDIATED COAGULATION: POSSIBLE ROLE AS A PHYSIOLOGIC ANTICOAGULANT. NS Key, K Immer, A Slungaard. University of Minnesota, Minneapolis, MN

PF4 is an abundant cationic platelet α-granule protein released during platelet aggregation. Because of its heparin-neutralizing effect, it has been proposed that PF4 propagates clot extension in the vicinity of platelets. Conversely, however, PF4 also inhibits Hageman factor activation, and we have recently shown that it amplifies activation of protein C by the thrombomodulin-thrombin complex up to 25-fold (in press). We hypothesized that PF4 may exert a direct anticoagulant action by interfering with clotting initiated by TF, the principal physiologic coagulation activator. In a modified prothrombin time assay, we find that 100 μg/ml PF4 prolongs plasma clotting initiated by human brain TF (3ng/ml) from 32 ± 1 to 48 ± 4 sec with an ED_{50} of 40 μg/ml. PF4 also prolongs the plasma clot time when cultured fibroblasts were used as the TF source (34 to 42 sec). Similarly, when plasma factor X is activated directly by Russell viper venom, PF4 prolongs the clotting time from 25 to 45 sec. By contrast, PF4 has no effect on the thrombin time assay, suggesting that these effects are not explained by inhibition of fibrinogen cleavage or of fibrin polymerization. Using purified coagulation proteins (TF 1ng/ml, VIIa 5nM, X 1.5μM) with 0.1 μM phosphatidylserine-phosphatidylcholine (PS/PC) vesicles in a chromogenic assay system, 100 μg/ml PF4 strongly inhibits Xa generation by approximately 85% (ED_{50}:10-30 μg/ml). At the same concentration, PF4 inhibits thrombin generation by the prothrombinase complex (5 nM Xa, 2.5 nM Va, II 35 μg/ml, 0.25μM PS/PC vesicles) from 9.1 to 4.5 nM IIa/min. We conclude that PF4 impairs TF-initiated clotting by inhibiting both the extrinsic Xase and prothrombinase complexes, possibly through interactions with anionic phospholipids. Based on these findings, we speculate that PF4 may play a hitherto unsuspected anticoagulant role in the physiologic regulation of clotting.

EARLY DETECTION OF THE DEVELOPMENT OF IRON DEFICIENCY BY PATIENT-SPECIFIC SEQUENTIAL ANALYSIS OF HEMATOLOGICAL TESTS GD McLaren,** CE McLaren,* EL Kambour,* HC Lukaski,* L Xia,* GJ McLachlan,* and GM Brittenham,** Veterans Affairs Medical Center and University of North Dakota, Fargo, ND; Moorhead State University, Moorhead, MN; USDA, ARS, Grand Forks Human Nutrition Research Center, Grand Forks, ND, University of Queensland, Brisbane, Australia; Case Western Reserve University, Cleveland, OH.

In established iron deficiency anemia, characteristic changes in hematological tests are helpful in suggesting the diagnosis, but the first detectable change after iron (Fe) stores have been exhausted is a decrease in hemoglobin concentration (Hb) or hematocrit (Hct). Tests of iron status such as serum ferritin and transferrin saturation are useful in detecting decreased Fe stores but are not routinely performed in the absence of anemia. We developed new methods for patient-specific analyses of laboratory tests using hierarchical multiple regression modeling to detect significant changes in sequential measurements. We studied 7 female and 4 male healthy human volunteer subjects during Fe depletion by serial phlebotomy to evaluate these statistical methods under controlled conditions. An average volume (± 1 SD) of 1455 ± 883 mL of blood was removed over 36 ± 18.6 days, accompanied by a decrease in hemoglobin from 14.3 ± 1.2 g/dL to 11.5 ± 1.2 g/dL and a post-phlebotomy serum ferritin of 6.9 ± 2.3 μg/L. Sequential measurements of Hb, Hct, mean cell volume (MCV), red cell distribution width (RDW), and red blood cell (RBC) volume distribution were performed throughout the study period. Statistically significant changes ($P<0.05$) were detected in Hb, Hct, and RBC volume distribution for all volunteers, in MCV for 9/11, and in RDW for 8/11. Significant departures from past values could be identified in at least one laboratory test for 10/11 subjects, even when values were still within the population reference ranges. Thus, patient-specific sequential analysis can facilitate early detection of changes in hematological measurements in evolving iron deficiency anemia.

HYPOFIBRINOLYSIS, HIGH LIPOPROTEIN (A) AND ISCHEMIC STROKE. CJ Glueck, MH Rorick*, M Schmerler*, J Anthony*, J Feibel*, M Bashir*, HI Glueck*, D Stroop*, T Hamer*, T Tracy*. Cholesterol Center, Jewish Hospital, Cincinnati OH.

In 87 patients, studied on average 1 yr after their strokes, 77% with ischemic strokes, we assessed the prevalence of hypofibrinolysis and high Lp(a) as stroke risk factors. There were 4 major findings: 1) Hypofibrinolysis was common, with bottom decile stimulated tissue plasminogen activator activity (tPA-Fx) found in 21% of stroke pts and in 30% of their 1st degree relatives compared to 7% of 29 normolipidemic controls ($p=.09,.026$). 2) The hypofibrinolysis was mediated by top decile levels of plasminogen activator inhibitor activity (PAI-Fx) found in 20% of stroke pts and in 21% of their 1st degree relatives versus 8% of 175 normolipidemic controls ($p=.007,.04$). Mean PAI-Fx and plasminogen activator inhibitor antigen were higher in stroke pts (18 U/ml, 35 ng/ml) than in the 175 normolipidemic controls (14 U/ml, $p=.02$; 28 ng/ml, $p=.016$). 3) Tissue plasminogen activator antigen, a probable marker for atherosclerosis, was much higher in stroke pts than in the 175 normolipidemic controls (15±7 ng/ml vs. 7±4, $p=.0001$). 4) High Lp(a) (>35 mg/dl) was common in stroke pts (48%) vs. 20% of 398 hyperlipidemic controls ($p=.0001$). In patients with ischemic stroke, hypofibrinolytic and high Lp(a) stroke risk factors are common, often familial, and should be routinely quantitated and treated.

FAILURE OF ERYTHROPOIETIN TO CORRECT INHIBITION OF ERYTHROID COLONY FORMATION BY β-INTERFERON IN VITRO. **RT Means Jr., Hematology/Oncology Division, University of Cincinnati College of Medicine and VA Medical Center, Cincinnati OH**

The anemia of chronic disease (ACD) results from cytokines mediating inflammation, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). Recombinant erythropoietin (rEPO) therapy corrects ACD in some cases. We have previously reported that the inhibitory effects of TNF and IL-1 on human erythroid colony forming units (CFU-E) are both indirect, that the effect of TNF is mediated by β-interferon (IFN; J Clin Invest 91:416, 1993), that the effect of IL-1 is mediated by γIFN (J Cell Physiol 150:59.1992), and that the in vitro effect of γIFN can be corrected by rEPO (Blood 78:2564,1991). We now report the effects of rEPO on inhibition of CFU-E by βIFN in vitro. βIFN inhibited CFU-E colony formation in a dose dependent manner. rEPO at concentrations up to 100 U/ml failed to correct inhibition of CFU-E colony formation in vitro by βIFN 100 U/mL. Inhibition of CFU-E by βIFN at lower concentrations of 10 U/mL and 50 U/mL also failed to reverse with rEPO 100 U/mL. In conclusion, the two in vitro models for ACD we have described (IL-1/γIFN and TNF/βIFN inhibition of CFU-E colony formation) exhibit differing responses to rEPO, suggesting that variable responses of ACD patients to rEPO may reflect the pattern of cytokine activity in the associated diseases.

ERYTHROID-SPECIFIC ALTERNATIVE PROCESSING OF HUMAN β SPECTRIN I PRE-mRNA: COMPETITION BETWEEN POLYADENYLATION AND SPLICING PATHWAYS. Chu Z-L, Winkelmann JC. University of Cincinnati, Cincinnati, OH

We are interested in the tissue-specific post-transcriptional control of gene expression in erythroid cells. The erythroid isoform of β spectrin I is unique to the red cell as a result of erythroid-specific pre-mRNA processing (*JBC* 265:20449, 1990; *Genomics* 18:118, 1993; *Blood*, 1994, in press). Our experiments are designed to elucidate the molecular basis of regulated pre-mRNA processing of β spectrin as a model for this type of gene regulation in erythroid cells. In erythroid cells, β spectrin I transcripts are cleaved and polyadenylated at the end of exon 32. Within exon 32, there is a donor splice site that is utilized in nonerythroid cells to splice in four additional exons, affecting the C-terminus of the resultant spectrin protein. Using the 3' end of the human β spectrin I gene, we developed a minigene transfection assay system to mimic erythroid-specific pre-mRNA processing in transfected cells. Several mutant minigenes were assembled in eukaryotic expression vectors to localize the *cis* determinants of erythroid-specific processing. These constructs were transfected into both erythroid and nonerythroid cell lines. Their processing patterns were analyzed by S1 nuclease protection. We were able to reproduce tissue-specific processing in transfected cells. We reduced the minigene by deletion to determine the minimal elements required for specific processing. However, when the 3' splice site of the first nonerythroid exon was ablated, erythroid-type cleavage/polyadenylation was detected in nonerythroid cells. These results indicate that 1) nonerythroid cells do not possess a inhibitory factor to block the usage of the erythroid-specific poly(A) site, and 2) the splicing pathway directly competes with the polyadenylation reaction. Erythroid-specific β spectrin I pre-mRNA processing may result, in part, from up-regulation of polyadenylation at the exon 32 site. Nonerythroid cells are capable, however, of using this site when splicing is inactivated. Perhaps erythroid cells directly inhibit the nonerythroid splicing pathway. Further characterization of erythroid-specific β spectrin I pre-mRNA processing may have broad implications for erythroid gene expression and erythroid development.

RADIOIMMUNOTHERAPY OF REFRACTORY B-CELL LYMPHOMA WITH 131-I-ANTI-B1 (ANTI-CD20) ANTIBODY. MS Kaminski, M Fenner,* KR Zasadny,* AW Milik, CW Ross,* IR Francis,* J Burgess,* J Estes,* S Crawford,* P Hodul,* R Cook,* D Regan,* N Petry,* S Glenn,* G Butchko,* RL Wahl,* University of Michigan, Ann Arbor, MI and Coulter Corp., Miami, FL.

We recently reported a high response rate accompanied by minimal toxicity in 10 chemotherapy-refractory B-cell lymphoma patients (pts) entered onto an ongoing phase I trial of an anti-CD20 mouse monoclonal antibody (anti-B1) labeled with 131-I (N Engl J Med 329: 459, 1993). 27 pts are now fully evaluable. All pts had failed prior treatments with chemotherapy (mean no. of prior regimens = 3) and had progressing tumors which were CD20 antigen-positive. All received between 1 and 3 tracer-labeled doses i.v. (5 mCi on 15 mg) spaced at weekly intervals which were immediately preceded by no pretreatment with unlabeled antibody (n = 21), or pretreatment with 135 mg (n = 23), or pretreatment with 685 mg (n = 15). The unlabeled antibody pretreatment dose resulting in optimal tumor dosimetry in these tracer studies was then used in a radioimmunotherapy (RIT) dose. The mCi amount given for RIT was based on tracer-projected whole-body radiation dose. Dose escalation proceeded in 10 cGy whole-body dose increments, beginning at 25 cGy, and included at least 3 pts at each level. 21 of the 27 pts received RIT, 6 leaving the protocol for varying reasons during tracer studies. Whole-body RIT doses ranged from 25 to 85 cGy (34 to 153 mCi). 18 of the 21 pts who received RIT (86%) achieved either complete remissions (12 pts) or partial responses (6 pts). Two patients who received only tracer doses also had partial responses. Responses were frequently observed during tracer studies, but the most rapid phase and the greater proportion of the response generally occurred after RIT. The complete remissions have been durable (six lasting 8 - 16 mos, six still in remission 4 - 15 mos). Toxicity has been modest, with grade 3 toxicity (myelosuppression) seen in 5 pts (lasting < 2 weeks in 4 pts). No opportunistic infections or instances of hypothyroidism have been observed. These results confirm that 131-I-anti-B1 RIT is indeed an effective new treatment for non-Hodgkin's B-cell lymphoma with minimal toxicity. Dose escalation continues in this trial to establish the maximum tolerated radiation dose of 131-I anti-B1 for RIT.

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Yttrium-90-labeled Anti-CD20 Monoclonal Antibody Therapy of Recurrent B-Cell Lymphoma[1]

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ABSTRACT

A Phase I/II dose escalation study of ^{90}Y-murine anti-CD20 monoclonal antibody (mAb) in patients with recurrent B-cell lymphoma was performed. The primary objectives of the study were: (*a*) to determine the effect of the preinfusion of unlabeled anti-CD20 mAb on the biodistribution of ^{111}In-anti-CD20 mAb; (*b*) to determine the maximal tolerated dose of ^{90}Y-anti-CD20 mAb that does not require bone marrow transplantation; and (*c*) to evaluate the safety and antitumor effect of ^{90}Y-anti-CD20 mAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's lymphoma were treated. Biodistribution studies with ^{111}In-anti-CD20 mAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of ~13.5, 20, 30, 40, and 50 mCi ^{90}Y-anti-CD20 mAb. Three patients were retreated at the 40-mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of ^{90}Y-anti-CD20 mAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3–29+ months following treatment. Radioimmunotherapy with ≤50 mCi ^{90}Y-anti-CD20 mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of ≤40 mCi ^{90}Y-anti-CD20 mAb were not myeloablative.

INTRODUCTION

Most patients with recurrent B-cell lymphoma are generally considered to be incurable with standard chemotherapy (1), and new therapies are needed for this disease. Encouraging results have been obtained in clinical studies using unlabeled anti-idiotype and *pan*-B mAbs[3] for the treatment of patients with recurrent B-cell lymphoma (2–8). Although clinical responses have been observed using unlabeled mAb (2–8), they have been limited by a number of factors (9), including: (*a*) heterogeneity of antigen expression on tumor cells, (*b*) inaccessibility of tumor cells, and (*c*) failure of host effector mechanisms to eliminate mAb-coated cells. The use of radiolabeled mAb (RIT) may solve some of these problems, because the local emission of ionizing radiation by radiolabeled mAb may kill cells with or without expression of the targeted antigen that are in close proximity to bound antibody. Similarly, the relatively penetrating radiation associated with radiolabeled mAb may overcome the problem of limited access in bulky or poorly vascularized tumors. In addition, host effector mechanisms are not required for tumor cell killing by RIT. The above factors combined with the inherent radiosensitivity of lymphoma cells make lymphoma an ideal disease to treat with RIT.

RIT in patients with recurrent B-cell lymphoma has resulted in durable clinical responses with a relatively high response rate (9–25). One of the most promising mAbs for the RIT of non-Hodgkin's lymphoma is the anti-CD20 mAb (9), which does not react with normal cells other than B lymphocytes, reacts with a nonmodulating antigen that does not undergo endocytosis, and is expressed at a relatively high density on targeted lymphoma cells (9, 26–28). RIT studies in non-Hodgkin's lymphoma have used ^{131}I and ^{90}Y primarily (9). These two radionuclides differ from one another, in that ^{131}I has a half-life of 193 h and a large component of γ emissions (81% with an energy of 0.364 MeV), whereas ^{90}Y is a pure β emitter with a half-life of 64 h, a maximum energy of 2.28 MeV, and an average energy of 0.935 MeV. The mean ranges of the β particles from ^{131}I and ^{90}Y in tissue are ~0.4 and ~2.5 mm, respectively. The path length over which 90% of the emitted energy is absorbed is 0.8 mm for ^{131}I and 5.3 mm for ^{90}Y (26, 29, 30). In theory, the emission properties and decay mode of

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[3] The abbreviations used are: mAb, monoclonal antibody; RIT, radioimmunotherapy; MeV, million electron volt; BM, bone marrow; BMT, BM transplantation; PSC, peripheral stem cell; G-CSF, granulocyte colony-stimulating factor; HAMA, human antimouse antibody; CHOP, cyclophosphamide-adriamycin-vincristine-prednisone; PR, partial response; CR, complete response; L-spine, lumbar spine; CT, computed tomographic; PD, progressive disease; FFP, freedom from progression; ANC, absolute neutrophil count; PRBC, packed RBC.

Table 1 Patient profile

Patient[a]	Sex/Age (y)	Dose (mCi ^{90}Y/ mg mAb)	Tumor histology[b]	Stage[c]	Prior therapy[d]	Volume of Tumor before treatment (g)	BM involvement (%)
1	M/37	13.6/85	FSC	IVE	ChlVP × 15, CVP, anti-ID + IFN, XRT, anti-ID + chl, MINE × 6, ESHAP × 3, C2B8	86	0
2	M/60	13.5/2	FSC/FM	III	chl/ID vacc, CP × 7, ID vacc, CP/ V/CVP, anti-ID, ONCEP × 6	<25	<5
3	M/48	13.7/106	FM	IV	CHOP × 10 +, CHAD × 3 +, CVP × 1	65	10
4	F/53	21.6/78	FSC	IA	XRT, CHOP × 1, CVP × 4, Flu/E, CEP	>500	0
5	M/58	20.0/99	FM	IV	CVP × 8, Chl, CHOP × 5, IFN × 10m, CVP × 2, XRT	58	0
6[e]	M/62	22.2/70	FSC	IIIA	CVP × 6, XRT, CHOP × 10, CEPP	65	0
7[e]	F/48	40.0/180 21.3/55 40.0/140	FSC	IV	CVP × 6	106 133	0
8	F/45	31.1/57.5	F + DM	IVA	CHOP × 4	162	
9[e]	M/50	31.4/99 43.7/94	MC	IV	MACOP-B, Chl, anti-ID, P/CVP, C2B8, P × 4	64/0 >500	0 20
10	M/49	32.6/112	FSC FLC	IV	MACOP-B	399	
11	M/39	41.6/93	FSC	IVA	Chl × 2, CHOP × 8, Chl × 2/Flu × 5	80 61	<10 0
12	M/54	41.6/80	FSC	IV	VACOP-B/B/Chl, splenectomy	82	10
13	M/69	43.5/188	SL	III	Chl/P, CVP, Flu, C2B8	435	10–20
14	M/53	42.0/290	FM	IVA	Chl/P, CVP, CHOP × 6, 2CDA × 2, XRT, CHOP × 3, P	258	<5
15	F/38	51.7/76	FSC	IVA	CHOP × 8, DICE × 3	292	<10
16	F/56	53.0/72	F + DM	IVA	CHOP × 2, XRT, CEPP × 7, Flu ×, CHOP × 6	110	0
17	F/43	53.4/208	FSC	IIIA	CVP × 6, Chl/P, CVP × 2	58	10
18	M/56	52.9/245	SL	IIIA	CHOP × 6, Flu × 3, C2B8	224	0

[a] Patients 1–4 were treated with B1 (Coulter Immunology), and patients 5–18 were treated with IDEC-Y2B8 (IDEC Pharmaceuticals Corporation).

[b] Tumor histology: FSC, follicular small cleaved; FM, follicular mixed; DM, diffuse mixed; MC, mantle cell; FLC, follicular large cell; SL, small lymphocytic.

[c] Pathological stage at diagnosis.

[d] Prior therapy: chl, chlorambucil; V, vincristine; P, prednisone; C, cyclophosphamide; anti-ID, anti-idiotype mAb; XRT, radiation therapy; MINE, Mesna (sodium 2-mercaptoethane sulfonate)–ifosfamide–mitoxantrone (Novantrone)–etoposide (VP-16); ESHAP, etoposide–solumedrol–Ara-C–cisplatinum (cisplatin); C2B8, chimeric anti-CD20 mAb (IDEC Pharmaceuticals Corp.); ID vacc, idiotype vaccine; CP, cyclophosphamide–prednisone; ONCEP, vincristine (O)–mitoxantrone (N)–cyclophosphamide–etoposide–prednisone; CHOP, cyclophosphamide–Adriamycin–vincristine–prednisone; CHAD, cisplatin–Ara-C–dexamethasone; Flu, fludarabine; E, etoposide; CEP, cyclophosphamide–etoposide–prednisone; CEPP, cyclophosphamide–etoposide–prednisone–procarbazine; MACOP-B, methotrexate–leukovorin–Adriamycin–cyclophosphamide–vincristine–prednisone–bleomycin; VACOP-B, etoposide–Adriamycin–cyclophosphamide–vincristine–prednisone–bleomycin; 2-CDA, 2-chlorodeoxyadenosine; DICE, dexamethasone–ifosfamide–carboplatin–etoposide.

[e] Patient profile prior to the second treatment in patients retreated once with ^{90}Y-anti-CD20 mAb.

^{90}Y should result in relatively higher tumor doses that may be more homogeneous in distribution than those obtained with ^{131}I-labeled mAb. Other potential advantages of ^{90}Y-labeled mAb include the associated minimal amount of penetrating radiation (resulting from bremsstrahlung), which allows for outpatient administration of relatively high doses and decreased contamination hazards because of the reduced urinary excretion compared with ^{131}I-labeled mAb.

In the Phase I/II study reported here, patients with recurrent B-cell lymphoma were treated with ^{90}Y-anti-CD20 mAb. The dose was escalated throughout the study between patient groups until a dose level was reached at which one or more patients required reinfusion of PSC for rescue from potentially lethal myelosuppression. The primary objective of the study was to evaluate the safety, biodistribution, and efficacy of ^{90}Y-anti-CD20 mAb in this patient population.

MATERIALS AND METHODS

Patients. Eighteen patients were treated in the study. Patients 1–4 were imaged and treated using B1 (Coulter Immunology, Hialeah, FL), and patients 5–18 were imaged using IDEC-IN238 and treated with IDEC-Y2B8 (IDEC Pharmaceuticals Corp., San Diego, CA). Six of the patients were women, and 12 were men, ranging in age from 38 to 69 (mean, 53.5) years. The clinical profile of the patients, including the extent of disease prior to treatment (mean, 172-g; range, <25–500-g tumors) and their histories of prior therapy are summarized in

Table 1. All of the patients had relapsed low- or intermediate-grade non-Hodgkin's lymphoma. Eleven of the patients had extranodal disease, and four had splenomegaly. All patients had failed at least one course of conventional chemotherapy, and the majority of the patients had had multiple courses of prior therapy (mean, 2.9; range, 1–5 regimens). Seven of the patients were chemorefractory (no significant clinical response to the most recently administered course of chemotherapy), and one was relatively chemointolerant (history of prolonged myelosuppression and severe hemorrhagic cystitis following CHOP chemotherapy). Before entry in the study, patients had to meet the following eligibility criteria: (*a*) failure of conventional therapy of B-cell lymphoma of any histological subtype; (*b*) demonstrated reactivity (≥25%) with anti-CD20 mAb on a tissue biopsy or aspirate; (*c*) BM involvement of <25% total cellularity at the time of BM harvest or PSC collection, WBC count >2,500/mm^3, absolute granulocyte count >1,500/mm^3, and platelet count >80,000/mm^3; (*d*) measurable disease; (*e*) ≥18 years of age, physiological age ≤70 years with negative pregnancy test results in fertile women of reproductive age; (*f*) Karnofsky performance status >60 (Southwest Oncology Group, <4) and life expectancy >12 weeks; (*g*) no chemotherapy or radiotherapy within 30 days and no concurrent stem cell toxins; (*h*) ≤25% of active BM irradiated previously; (*i*) no prior BMT; (*j*) no allergy to mouse proteins; (*k*) patient acceptance by BMT physicians for BM harvest or PSC collection; (*l*) no significant illness that, in the opinion of the investigators, would compromise any aspect of the planned treatment or affect the ability of the patient to give informed consent; and (*m*) signed informed consent. Three patients (not included in Table 1) underwent imaging studies with ^{111}In-anti-CD20 mAb but did not receive therapeutic doses of ^{90}Y-anti-CD20 mAb because of an unacceptable biodistribution of ^{111}In-mAb (the estimated liver dose was >10 times the estimated whole body dose), progressive thrombocytopenia, or rapid disease progression.

Study Design. PSCs or autologous BM was harvested from all patients prior to treatment as described below. Two *in vivo* biodistribution studies using ^{111}In-anti-CD20 mAb were performed in each patient entered at dose levels of ≤30 mCi ^{90}Y-anti-CD20 mAb ~1 week apart. The first imaging study was performed without preinfusion of unlabeled mAb. This was followed by a second study in which 1 mg/kg unlabeled anti-CD20 mAb was preinfused immediately prior to administration of the ^{111}In-anti-CD20 mAb. Only one *in vivo* biodistribution study was performed in the patients treated with either 40 or 50 mCi ^{90}Y-anti-CD20 mAb. At each of these two dose levels, two patients received 1 mg/kg and two patients received 2.5 mg/kg unlabeled anti-CD20 mAb immediately prior to administration of the ^{111}In-anti-CD20-mAb. If acceptable biodistribution was obtained (defined below), a therapeutic dose of ^{90}Y-anti-CD20 mAb was administered within 1–2 weeks of completion of the dosimetric imaging studies. Unlabeled mAb was preinfused similarly prior to administration of the ^{90}Y-anti-CD20 mAb in all but one patient, because of improved mAb biodistribution obtained in the prior imaging study using preinfused, unlabeled mAb compared with administration of ^{111}In-mAb alone. Three to four patients were treated at each of the following dose levels of ^{90}Y-anti-CD20 mAb: ~13.5, 20, 30, 40, and 50 mCi. Following treatment, patients were followed closely as described below and supported with G-CSF and transfusions (PRBC and platelets) as indicated clinically. G-CSF and platelet transfusions were generally not used for >1 month without assessment of potential BM recovery (spontaneously increasing blood counts without support or signs of BM recovery on biopsy). Stored PSCs were reinfused when the ANC fell to <500/mm^3 for 3 consecutive days or platelets were <20,000/mm^3 despite G-CSF support and platelet transfusion. Patients without bulky disease that had responded to therapy (a ≥25% decrease in the sum of the products of all sentinel lesions) were eligible for retreatment on progression of disease (≥50% increase in the product of two dimensions of any one sentinel lesion, ≥25% increase in the sum of the products of all sentinel lesions, or the appearance of one or more new lesions), providing they continued to meet all of the eligibility criteria listed above. One patient (patient 9) with bulky disease (massive splenomegaly ≥750 g and total tumor burden ≥500 g before treatment) was retreated with an ongoing PR. HAMA assays with a sensitivity of 0.1–0.05 ng/ml were performed prior to each antibody infusion. Patients had to be HAMA negative to be treated.

Antibody and Radioimmunoconjugate Preparation. Patients 1–4 were treated with ^{90}Y-anti-CD20 mAb (B1), a murine IgG2a, produced by Coulter Immunology, under IND BB-3948. Patients 5–18 were treated with ^{90}Y-anti-CD20 mAb (IDEC-Y2B8), a murine IgG1, produced by IDEC Pharmaceuticals Corp. under Investigational New Drug number BB-4850. Both mAbs bind CD20, which is a M_r 35,000 cell surface phosphoprotein expressed by >95% of B lymphocytes and >90% of B-cell lymphomas. Both mAbs were chelated with isothiocyanatobenzylmethyl-diethylenetriaminepentaacetic acid with a molar ratio of ~1. All mAb preparations were tested for general safety, sterility, pyrogenicity, polynucleotides, mycoplasma, and adventitious virus contamination. The anti-CD20 mAbs were conjugated to ^{111}In (in 0.04 N HCl as cation, 10 mCi/ml) and ^{90}Y (in 0.04 N HCl as cation, 20 mCi/ml). The specific activity of the ^{111}In-labeled mAbs averaged 3.3 mCi/mg and ranged between 10.3 and 13.5 mCi/mg for the ^{90}Y-labeled mAbs. Radioincorporation of the radiolabeled mAb was determined by instant TLC in triplicate and averaged 94.0% for ^{111}In-mAb and 96.4% for ^{90}Y-mAb. Immunoreactivity of the radiolabeled mAbs was evaluated by binding assays using lyophylized PB-67 cells or cultured SB cells. The mean immunoreactivity was 85.6 ± 13.7% (range, 72.3–100%) for the ^{111}In-mAb and 74.9 ± 10.9% (range, 58.0–92.5%) for the ^{90}Y-mAb. Endotoxin levels of radiolabeled mAbs were evaluated by the Pyrogent Plus limulus amoebocyte lysate kit (BioWhittaker, Inc., Walkersville, MD). Typically, the assay sensitivity ranged between 0.25 and 0.125 endotoxin units/ml, and the labeled mAbs were always less than this level of endotoxin. Sterility of the radiolabeled mAb was determined retrospectively by direct inoculation of 1.0 ml mAb into screw-top medium tubes. Positive and negative controls were always included, and all assays were performed in duplicate. The inoculated trypticase soy broth (Baltimore Biological Laboratories; Becton Dickinson, Cockeysville, MD) was incubated at 25°C and examined for growth at days 3, 7, and 14. Inoculated thioglycolate media (Baltimore Biological Laboratories) were also incubated at 37°C and examined for growth at days 3, 7, and 14. All radiolabeled mAb

preparations were found to be sterile. The final radiolabeled mAb preparations were diluted with injectable 0.9% saline or PBS containing 5–7.5% human albumin (Baxter Healthcare Corp., Glendale, CA).

Autologous BM and PSC Collection. All patients underwent either autologous BM harvest or PSC collection as per the standard, ongoing BMT protocol at Stanford University Hospital. Briefly, BM harvest was performed under general anesthesia. Three core biopsies were obtained from each of the iliac crests, and multiple BM aspirations were performed from the right and left posterior iliac crests. The aspirate was mixed with heparinized RPMI 1640 media with a final concentration of 6–20 units/ml marrow. After filtering and processing, the cells were purged with anti-CD9, CD10, CD19, and CD20 mAbs and complement and frozen. PSC collections were also performed on these patients as a backup as described below.

Mononuclear cell pheresis was performed using either a COBE 2997 or a COBE Spectra machine (COBE BCT, Inc., Lakewood, CO). Multiple collections were performed, with the actual number per patient dependent on the peripheral mononuclear cell count. During each run, 8000 ml were exchanged, with an anticipated yield of 5×10^9 mononuclear cells. Before initiation of PSC collection, patients received G-CSF (5–10 μg/kg/day s.c.) for 4–6 consecutive days in order to increase the yield of mononuclear cells collected.

Biodistribution Studies. Immediately following administration of the unlabeled anti-CD20 mAb (0, 1, or 2.5 mg/kg), ~5 mCi (2 mg) ^{111}In-anti-CD20 mAb were injected as a slow i.v. push. *In vivo* biodistribution studies for dosimetric estimates were conducted in each patient as follows. Immediately following the ^{111}In-anti-CD20 (5-mCi) administration, patients were imaged in the anterior and posterior projections in a whole body area mode. Imaging was repeated 14–18, 24, 48, and 72 h after injection. Whole body average (effective) retention times were estimated using an existing algorithm based on single exponential analysis (with five points). The same was repeated for regions of interest. For recognizable organs or tumor lesions, appropriate regions of interest were drawn, and retention times were computed similarly. The total dose was expressed in camera cpm using the first (immediate postinjection) whole body counts. A region of interest was drawn around the head, trunk, and limbs and around recognizable organs (*e.g.*, heart, liver, spleen, and L-spine) and some tumors. Using an algorithm described previously (31), the regions were used to compute organ volumes, and concentrations (fraction of total dose/g) were calculated. Cumulative concentrations were then computed using a single exponential fit and a decay correction for ^{111}In, and estimated anticipated doses from ^{90}Y-anti-CD20 mAb were calculated using the K for ^{90}Y. mAb biodistributions were considered acceptable if in any organ or tissue (excluding the spleen or tumor) the estimated cumulative dose from ^{90}Y was less than 10 times the whole body dose, or if the estimated cumulative dose for the liver was <1500 cGy. Patients with acceptable biodistributions were then treated with ^{90}Y-anti-CD20 antibody. All patients with the exception of patient 2 were pretreated with unlabeled mAb. This particular patient did not receive a preinfusion of unlabeled mAb, because 1 mg/kg unlabeled mAb did not result in improved biodistribution, and the patient's splenic disease (discrete nodules) was visualized better without the preinfusion of unlabeled mAb.

PSC Reinfusion. PSC were reinfused in patients who met the criteria for transplantation as described above. Acetaminophen (650 mg), hydrocortisone (50 mg), and diphenhydramine (25 mg) were administered prior to the infusion of the PSC. All patients were monitored closely and received supportive care as indicated clinically.

Clinical Parameters Monitored. Following treatment, a number of parameters were followed. These included blood counts, chemistry panels, urine analyses, peripheral blood immunophenotyping, serum immunoglobulin quantitation, and HAMA tests. Patients were seen for follow-up examinations approximately every 1–2 months during the first year after treatment. The exact timing of these visits was determined in part by the patients' clinical status. The official follow-up period was defined as the time interval between treatment and progression of disease. Restaging was performed at the above follow-up visits and was based on physical examination, BM biopsies (if indicated), and a variety of radiographic studies, including chest and abdominal X-rays and CT scans. Response criteria were defined as follows. A CR was the disappearance of all clinically detectable tumor and no evidence of lymphoma on subsequent BM biopsy if initially present. A PR was a reduction by at least 50% from baseline in the overall tumor sizes of sentinel lesions (the sum of the products of the two longest perpendicular diameters of the sentinel lesions so designated prior to therapy), with no simultaneous increase in size of any other lesion or the appearance of new lesions. A minor response was a decrease of at least 25% from baseline in overall tumor sizes of sentinel lesions without an increase in the size of any other lesion or the appearance of new lesions. Patients with stable disease did not exhibit at least a 25% decrease or 25% increase in the overall sizes of sentinel lesions or a 50% increase in the size of any single lesion or develop any new lesions. PD was measured with reference to baseline values, unless a decrease in size had been observed, in which case progression was measured from the tumor size nadir. PD was defined as an increase of at least 25% in the sum of the sizes of all sentinel lesions, a 50% or greater increase in the size of any single lesion, or the appearance of a new lesion. Clinical responses often evolved over time, and the time to best response was defined as the time from treatment to the time at which the tumor size nadir occurred. FFP was measured from the treatment date to the date that PD was first documented.

HAMA Responses. HAMA levels were determined using an ELISA. Ninety-six-well microtiter plates were coated with murine anti-CD20 mAb. Fifty μl coat antigen solution [5 μg/ml in carbonate buffer (pH 9.6)] was dispensed in each well of a flat-bottom microtiter plate [Dynatech (Immunlon) Lab, Inc., Chantilly, VA]. Plates were washed five times with 0.05% Triton X-100 in PBS before use. Nonspecific protein-binding sites were blocked by filling wells with 2% BSA in PBS. Following incubation for 15–20 min at room temperature, plates were washed with 0.05% Triton X-100 in PBS. Serum samples were plated in serial dilutions in 2% BSA in PBS. Serum from a patient with a known HAMA response was used as a positive control. Plates were incubated at room temperature for 1 h and washed four times. Horseradish peroxidase-conjugated, goat antihuman λ chain (Sigma Chemical Co., St. Louis, MO) and κ

Table 2 Sites imaged

Patient[a]	No. of known disease sites[b]	No. of sites imaged: 0 mg unlabeled mAb	1 mg/kg unlabeled mAb	2.5 mg/kg unlabeled mAb
1	4	1	1	
2	3	3	3	
3	9	2	8	
4	7	0	3	
5	3	0	0	
6	4	2	3	
7[c]	6	0	5	
8	3	1	2	
9	13	1	1	
10	8	1	8	
11	8		4	
12	10		10	
13	10			9
14	6			5
15	7		0	
16	5		2	
17[c]	7			7
18[c]	3			3

[a] Patients 1–4 were treated with B1, and patients 5–18 were treated with IDEC-Y2B8.
[b] Based on the Ann Arbor staging system.
[c] Occult sites of disease were also imaged in these patients.

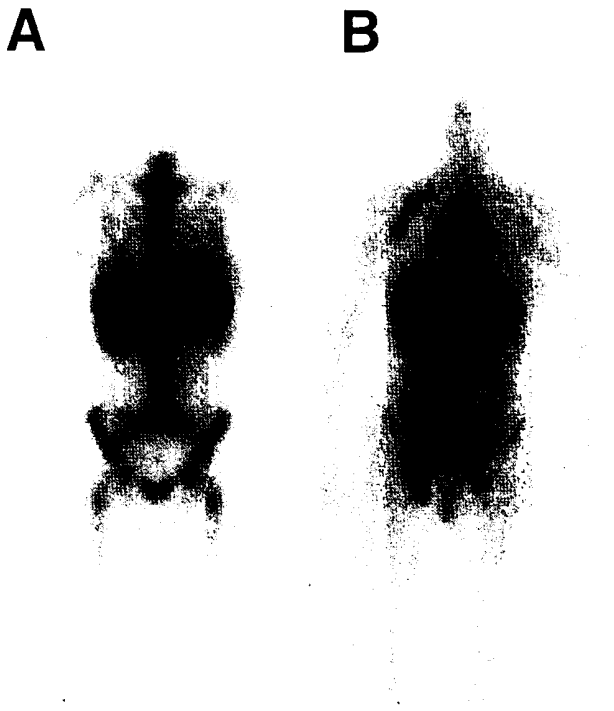

Fig. 1 Gamma camera images of patient 7 obtained 72 h following administration of ^{111}In-labeled mAb without the preadministration of unlabeled antibody (*A*) and following preinfusion of 1 mg/kg unlabeled antibody (*B*).

chain (Caltag Laboratories, South San Francisco, CA) antibodies were added [50 μl; 1:1 (v/v)] to each well at a final concentration of 1:2000 in 2% BSA and PBS. After a second incubation for 30 min, plates were washed four times, and 100 μl enzyme substrate solution [30% H_2O_2 (J. T. Baker Chemical Co., Phillipsburg, NJ); 3.5 μl/10 ml], 2,2′-azino-bis-(3-ethylbenzthiazoline sulfonic acid) [Sigma; stock, 15/mg/ml, 10 μl/ml in citrate buffer (pH 4.0)] were added to the plates. Plates were incubated at room temperature in the dark and read in an automatic ELISA kinetic microplate reader (Molecular Devices, Palo Alto, CA) or ELISA microtiter plate reader (Dynatech) at absorbance 405 nm.

RESULTS

Biodistribution. Biodistribution studies were obtained in all patients following the injection of ^{111}In-labeled anti-CD20 mAb. Whole body images were obtained immediately following injection of the radiolabeled antibody and thereafter at ~14–17, 24, 48, and 72 h after injection. The first 10 patients entered in the study underwent two biodistribution studies approximately 1 week apart. Their first study was performed without the preinfusion of unlabeled antibody, and the second study was performed using 1 mg/kg unlabeled antibody as a preinfusion immediately prior to administration of the ^{111}In-labeled antibody. The preadministration of unlabeled antibody resulted generally in improved biodistribution of the radiolabeled antibody with increased visualization of known sites of disease and decreased projected doses to the spleen and L-spine from the ^{90}Y-labeled mAb. Important determinants of biodistribution included not only the preadministration of unlabeled antibody but also the presence or absence of splenomegaly. Table 2 summarizes the effect of the preadministration of unlabeled antibody on the number of known disease sites imaged in the 18 patients treated in this study. In the absence of unlabeled antibody, only 18% of known sites of disease were imaged. Preadministration of 1 mg/kg unlabeled antibody resulted in imaging of 56% of known sites of disease, whereas 92% of known sites of disease were imaged well following the preadministration of 2.5 mg/kg unlabeled antibody immediately prior to the injection of the ^{111}In-labeled antibody. Furthermore, not only were more disease sites imaged in these patients generally, but the intensity of imaging tended to be higher following the preinfusion of unlabeled antibody, and occult sites of disease (nodal sites not enlarged on CT scans) were imaged as well in several patients. An example of the improved biodistribution obtained following the administration of 1 mg/kg unlabeled antibody is shown in Fig. 1. These images were obtained 72 h following the injection of ^{111}In-anti-CD20 mAb approximately 1 week apart. Fig. 1*A* shows the 72-h image obtained without the preadministration of unlabeled antibody, and Fig. 1*B* shows the image obtained following preinfusion of 1 mg/kg unlabeled antibody There is a

Fig. 2 Gamma camera images of patient 9 obtained 72 h following administration of ^{111}In-labeled antibody prior to the patient's initial treatment (*A*), which resulted in a marked reduction in spleen size, and prior to the patient's second treatment with ^{90}Y-labeled antibody (*B*).

striking difference between the two studies in the number of known sites of disease visualized. The presence of splenomegaly was also an important determinant of the subsequent biodistribution of radiolabeled antibody. Known sites of disease were generally visualized poorly in patients with splenomegaly. The effect of splenomegaly on the biodistribution of the antibody can be seen clearly in Fig. 2, showing images obtained 72 h after the administration of ^{111}In-labeled antibody preceded by 1 mg/kg unlabeled antibody. This particular patient was treated twice; Fig. 2*A* shows the 72-h image obtained prior to the patient's initial treatment, and Fig. 2*B* shows the 72-h image obtained prior to the patient's second treatment. The patient had a PR following the first treatment, with a marked reduction in spleen size. This resulted in significantly improved biodistribution of the radiolabeled antibody prior to retreatment with improved visualization of known sites of disease.

Dosimetry. Dose estimates based on ^{111}In-labeled imaging studies for anticipated doses from the ^{90}Y-labeled antibody (cGy/mCi) are shown in Table 3 for all 18 patients (exclusive of retreatments). All dose estimates are for the conditions used for administration of the therapeutic dose of ^{90}Y-anti-CD20 antibody (all with the preinfusion of unlabeled antibody except for patient 2, because discrete splenic nodules in that patient were visualized better in the absence of additional unlabeled antibody). Mean doses ± SDs are shown for the whole body, cardiac blood pool, liver, spleen, L-spine, and tumor. The SDs are relatively large because of considerable interpatient variability in antibody biodistribution. The SD for the spleen is particularly large, because two patients (patients 16 and 17) with presumed splenic disease and splenomegaly prior to treatment had larger proportions of the injected doses localize in their spleens than those observed in many of the other patients studied. The anticipated mean tumor dose was ~26.9 cGy/mCi with a large SD because of an unusually high tumor dose estimated for patient 6 (193.3 cGy/mCi, average of estimates for two separate small lesions).

Table 4 shows similar dosimetric calculations for the first 10 patients imaged both with and without unlabeled antibody. The values in this table represent paired observations in which two studies were performed in each of these 10 patients. Preinfusion of unlabeled antibody had little impact on estimated doses to the whole body, cardiac blood pool, liver, and L-spine. The most marked effect on organ dosimetry was in the spleen, in which preinfusion of unlabeled antibody resulted in a decrease in the mean projected dose from 44.7 to 10.3 cGy/mCi. Preinfusion of unlabeled antibody also resulted in an increase in the mean projected tumor dose from 16.5 to 40.3 cGy/mCi. The difference in biodistribution with and without the preinfusion of unlabeled antibody is primarily due to an increase in the cumulative concentration of the radiolabeled antibody in plasma (mean percentage of total dose × h in plasma with no unlabeled antibody = 2442 ± 3356 *versus* 5458 ± 3063 following preinfusion of unlabeled antibody; $P < 0.005$), decreased renal excretion (34.3 ± 25.3% excreted by 72 h without preinfused unlabeled antibody *versus* 21.1 ± 17.1% excreted by 72 h following preinfusion of unlabeled antibody; $P < 0.05$), and a relative increase in the uptake of radiolabeled antibody in disease sites following preinfusion of unlabeled antibody ($P = 0.27$). Interestingly, ANOVA failed to show any statistically significant differences ($P \leq 0.05$) between the cumulative concentration of radiolabeled B1 compared with radiolabeled 2B8 in plasma and the whole body (data not shown). In addition, there were no statistically significant differences between the cumulative concentrations of ^{111}In-B1 and ^{90}Y-B1 and between the cumulative concentrations of ^{111}In-238 and ^{90}Y-2B8 in plasma (data not shown). This is important, because the biodistribution of the ^{111}In-labeled mAb is used to predict the dosimetry from the ^{90}Y-labeled mAb (which is difficult to assess directly from the associated bremsstrahlung), and because the relative stability and bioactivity of ^{90}Y and ^{111}In chelates are usually similar but may not be identical.

Toxicity. The nonhematological toxicity observed following administration of a therapeutic dose of ^{90}Y-anti-CD20 mAb is summarized in Table 5. Antibody infusions were well tolerated, and nonhematological toxicity was generally mild (grades 1 and 2). Of note, rashes occurred usually immediately following antibody infusions and resolved generally ~2 h following administration of antihistamines. The majority of grade 1 fevers were less than 37.5°C. Two of the three grade 1

Table 3 Dosimetry (cGy/mCi) of ^{90}Y-anti-CD20 for all patients (mean ± SD)

Organ	Dose groups (mCi)					All patients
	13.6	21.2	31.7	42.9	52.7	
Whole body[a]	1.3 ± 0.3	2.3 ± 1.1	1.0 ± 0.7	1.4 ± 0.4	1.3 ± 0.5	1.5 ± 0.8
Cardiac blood pool	8.4 ± 4.2	11.5 ± 5.0	5.9 ± 3.0	10.2 ± 1.8	9.1 ± 8.0	9.2 ± 4.8
Liver	8.3 ± 2.3	9.3 ± 5.1	8.7 ± 2.9	8.7 ± 4.0	13.9 ± 11.1	9.9 ± 6.0
Spleen	16.4 ± 19.2	14.7 ± 7.8	7.4 ± 1.7	13.3 ± 16.8	118.1 ± 93.7[b]	31.7 ± 54.0
Tumor	7.5 ± 3.6	89.8 ± 91.3[b]	18.3 ± 16.2	12.1 ± 4.4	11.7 ± 9.4[b]	26.9 ± 46.3

[a] Whole body − regions of interest = residual whole body dose.

[b] Based on three of four patients treated at that dose level, because tumors or the spleen were too poorly imaged in one of four patients to compute an estimated dose.

infections consisted of a tooth abscess and chronic sinusitis, which, in retrospect, predated treatment. The third grade 1 infection was a mild upper respiratory infection. The five recorded grade 2 infections included infections in two of the three patients that were retreated at the 40-mCi dose level. The other three grade 2 infections occurred in patients treated with single doses of 50 mCi ^{90}Y-labeled antibody. Three of these five patients had readily identifiable sources of infection (middle ear, skin, and sinus), whereas two patients presented with fever and neutropenia with no identifiable sources (all cultures were negative) and were treated with i.v. antibiotics. In one of the patients with fever and neutropenia, the fever was thought to be related to the tumor, because the patient had rapid PD following retreatment. All of the fevers and infections resolved following antibiotic therapy. None of the patients had significant reductions in immunoglobulin levels following treatment. Four patients developed positive HAMA titers 4 (patient 10), 5 (patients 8 and 17), and 11 (patient 3) months after treatment.

Hematological toxicity was more severe and is summarized in Table 6, in which the numbers of patients with grades 1–4 leukopenia, granulocytopenia, thrombocytopenia, and anemia are shown. As can be seen, there were more patients with grade 4 thrombocytopenia than grade 4 granulocytopenia. Nadir ANCs and platelet counts are shown as a function of dose in Fig. 3, *A* and *B*. There was generally an inverse relationship between dose and nadir blood counts, with the exception of the group treated with ~40 mCi ^{90}Y-anti-CD20. These patients had received less prior cytotoxic therapy than the patients treated at the other dose levels, with an average of only 1.5 previous courses of chemotherapy. This group had presumably more BM reserve than the other groups, as reflected by higher ANCs than the group treated with ~30 mCi. Furthermore, a smaller proportion of the patients treated at the 40-mCi dose level required platelet transfusions than that in the 30-mCi dose group, and none of the patients treated with 40 mCi required PRBC transfusions, whereas two patients treated at the 30-mCi dose level required PRBC transfusion. The mean WBC and platelet nadir, time of onset, and duration of nadir are shown in Table 7. Mean nadir counts are based on absolute nadir counts or the lowest count that occurred prior to the initiation of G-CSF or platelet transfusions. The duration of blood count nadirs is the total time

Table 4 Dosimetry (cGy/mCi) of ^{90}Y-anti-CD20 for paired observations (mean ± SD)

	0 mg unlabeled mAb	1 mg/kg unlabeled mAb	Difference
Whole body	1.9 ± 1.0	2.6 ± 2.3	−0.7
Whole body (residual)[a,b]	1.2 ± 0.5	1.7 ± 0.9	−0.5
Cardiac blood pool[b]	6.6 ± 3.1	8.9 ± 4.5	−2.3
Liver	7.1 ± 3.1	8.7 ± 3.5	−1.6
Spleen[b]	44.7 ± 53.0	10.3 ± 6.2	34.4
L-spine	10.4 ± 8.3	8.9 ± 4.7	1.5
Tumor	16.5 ± 10.4	40.3 ± 59.7	−23.8

[a] Whole body − regions of interest (cardiac blood pool, liver, spleen, L-spine, and tumor) = residual whole body dose.

[b] $P < 0.10$ but > 0.05 for estimated doses with 0 mg unlabeled mAb compared with 1 mg/kg unlabeled mAb.

Table 5 Number of Patients with nonhematological toxicity by grade

Toxicity	Grade			
	1	2	3	4
Hypotension	0	2		
Tachycardia	1			
Skin reaction[a]	4			
Fever	12	2		
Chills	2			
Myalgias	1			
Mucosal symptoms	1	1		
↑ Liver function tests[b]	1	1	1	
Headache	1			
Infection	3	5[c]		

[a] Includes two patients with pruritus but no rash.

[b] Elevated transminases (grade 1) occurred in one patient treated with 40 mCi ^{90}Y-anti-CD20 mAb 3 weeks after treatment and resolved over 2 weeks. Two patients had elevated bilirubin levels (grades 2 and 3) 3–4 weeks after treatment with 50 mCi ^{90}Y-anti-CD20 that returned to normal within 1 week without any intervention.

[c] Includes two retreated patients.

Table 6 Number of patients with hematological toxicity by grade

Hematological toxicity	Grade			
	1	2	3	4
Leukopenia	1	3	10	3
Granulocytopenia	0	3	9	4
Thrombocytopenia	5	1	3	9
Anemia[a]	2[a]	5	4	0

[a] One of two occurred after treatment; does not include patients with grade 1 anemia before treatment that did not progress to grade 2 toxicity after treatment.

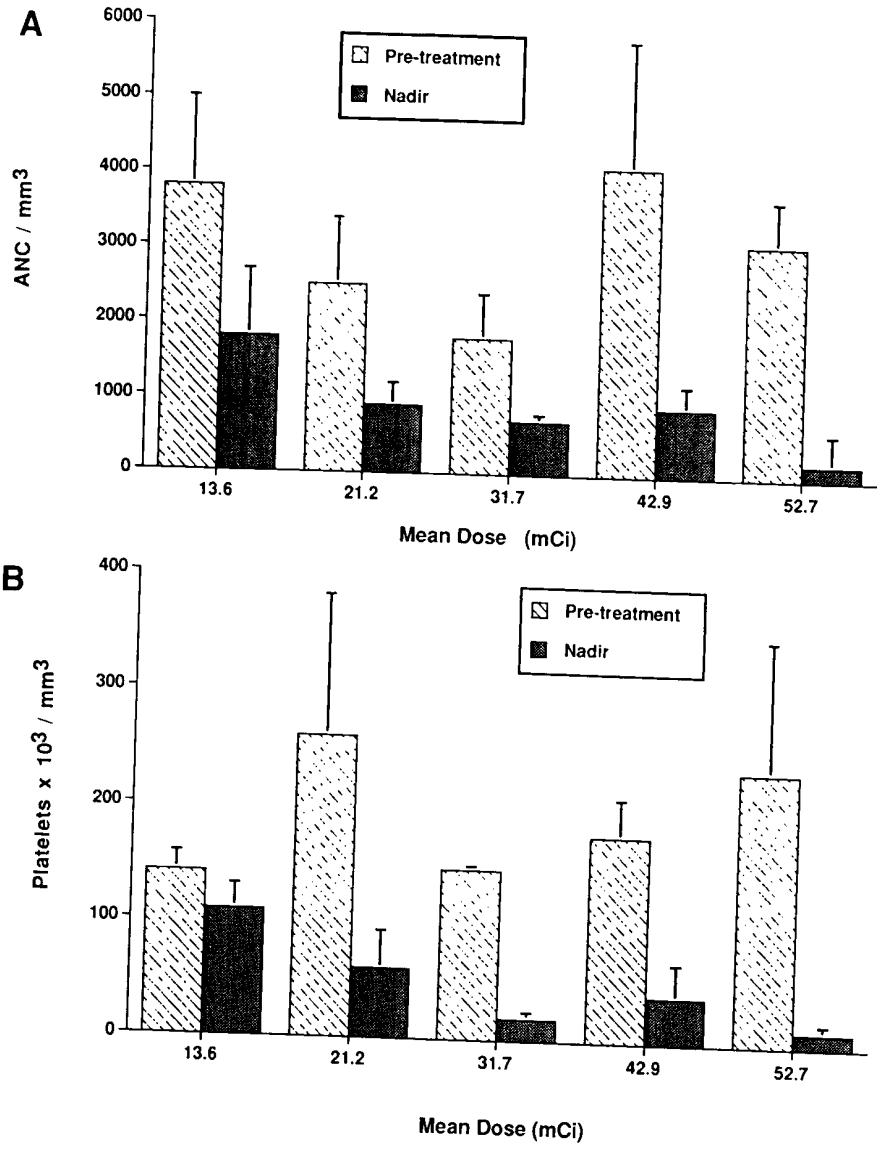

Fig. 3 *A*, ANCs; and *B*, platelet counts as a function of dose. Data are shown as the mean ± SD (*error bars*).

required for recovery of counts to pretreatment or normal levels and not the duration of time for which either G-CSF or platelet transfusions were required. In general, higher doses resulted in nadirs that occurred sooner, were more profound, and lasted longer. Two of the patients treated at the 50-mCi dose level required reinfusion of PSCs. Peripheral blood CD20 counts fell to very low or undetectable levels in most patients within 2–14 days of treatment, with recovery to approximately pretreatment or normal levels 2 weeks–5 months. CD20 counts returned to pretreatment levels in most patients within 3 months. In three patients, depletion of circulating B lymphocytes occurred following the dosimetry study prior to administration of ^{90}Y-anti-CD20 mAb.

Toxicity in the three patients who were retreated with ~40 mCi ^{90}Y-anti-CD20 mAb was more significant. Two of the three patients had grade 2 infections, as discussed previously. One patient with 34% of circulating tumor cells at the time of retreatment and considerable BM uptake of ^{111}In-labeled antibody on the pretreatment biodistribution study required reinfusion of PSCs. All three patients required G-CSF, and two of the patients required platelet and PRBC transfusions. In all three patients, posttreatment thrombocytopenia was more prolonged than following the first treatment and was more profound generally.

Clinical Responses. The clinical responses for patients treated with single doses of ^{90}Y-anti-CD20 mAb are summarized in Table 8. The actual dose administered is shown for each patient, as well as the subsequent best response, time to best response (which often evolved over time), and FFP in months. The overall response rate was 72%, with a CR rate of 33% and a PR rate of 39%, with FFP ranging between 3 and 29+ months. The patient with the ongoing CR at 29+ months is patient 2, who had the lowest pretreatment tumor burden of any of the patients treated in this study. The two patients with stable disease following treatment with ~50 mCi ^{90}Y-labeled mAb required PSC reinfusion. One of these patients had a reduction

Table 7 Blood count nadirs (mean ± SD)

Dose (mCi)	Pretreatment counts		WBC nadir			Platelet nadir		
	WBC	Platelets	Count	Onset (wk)	Duration (wk)[a]	Count	Onset (wk)	Duration (wk)[a]
13.6 ± 0.1 (N = 3)	6.3 ± 1.6	141 ± 17	3.4 ± 1.1	5.5 ± 3.5	3.3 ± 3.9	109 ± 22	5.5 ± 2.1	2.7 ± 2.9
21.2 ± 1.0 (N = 4)	3.6 ± 1.0	260 ± 122	1.6 ± 0.6[b]	6.6 ± 1.1	3.1 ± 1.3	60 ± 33	5.6 ± 0.5	3.6 ± 0.5
31.7 ± 0.8 (N = 3)	4.3 ± 1.0	146 ± 4	1.5 ± 0.3[c]	4.3 ± 2.0	7.3 ± 2.4	19 ± 6[d]	4.7 ± 0.3	5.3 ± 1.8
42.9 ± 0.9 (N = 4)	5.6 ± 1.2	177 ± 33	1.7 ± 0.5[e]	5.1 ± 0.5	3.8 ± 2.0	40 ± 29[f]	4.8 ± 0.9	3.5 ± 1.1
52.7 ± 0.7 (N = 4)	3.9 ± 0.8	235 ± 114	0.7 ± 0.8[g]	3.9 ± 1.8	5.4 ± 1.7	13 ± 7 [h]	3.6 ± 1.2	5.1 ± 2.3

[a] Total time required for recovery of counts to pretreatment/normal levels, not the duration of time for which G-CSF and/or transfusion support was required.
[b] Two patients required G-CSF.
[c] Three patients required G-CSF.
[d] Two patients required platelet transfusions, and two patients required PRBC transfusions.
[e] Three patients required G-CSF.
[f] Two patients required platelet transfusions.
[g] Four patients required G-CSF.
[h] Four patients required platelet transfusions, and three patients required PRBC transfusions.

Table 8 Clinical responses

Patient[a]	Dose ^{90}Y-anti-CD20 (mCi)	Response	Pretreatment % tumor volume remaining (g)		Time to best response (months)	FFP (months)
1	13.6	SD[b]	100	(86)		7
2	13.5	CR	0	(0)	3	29+
3	13.7	PR	46	(30)	2	5
4	21.6	SD	100	(>500)		6
5	19.9	SD	62	(36)		24+
6	22.2	PR	31	(20)	2	8[c]
7	21.3	CR	0	(0)	3	9[c]
8	31.1	CR	0	(0)	5	12
9	31.4	PR	38	(399)	2	3+[c]
10	32.6	PR	14	(11)	2	7
11	43.7	CR	0	(0)	3	12
12	41.6	PR	11	(9)	1	12
13	43.5	PR	21	(91)	1	3
14	42.9	CR	0	(0)	4	9
15	51.7	SD	39	(114)		2
16	53.0	SD	70	(77)		2
17	53.4	CR	0	(0)	3	6
18	52.9	PR	43	(105)	2	5.5

[a] Patients 1–4 were treated with B1, and patients 5–18 were treated with IDEC-Y2B8.
[b] SD, stable disease.
[c] Patients were retreated subsequently with ~40 mCi ^{90}Y-anti-CD20 mAb (IDEC-Y2B8).

of more than 50% in the total tumor size (sum of the product of the longest two perpendicular tumor dimensions for all known sites of disease), but because the percentage of tumor reduction was only 20% based on the two sentinel lesions identified by CT scan prior to therapy, the patient's overall response was scored as a minor response. The relatively poor responses of these two patients may be due, in part, to their bulky disease and low levels of CD20 expression on biopsied tumors (the lowest of any of the patients treated, with 61% and 64% reactivity, respectively). In addition, one of these two patients was among the two most heavily pretreated patients in the series, and known sites of disease were visualized poorly in both of these patients, with no known sites of disease imaged in one patient, and only two sites of disease imaged poorly in the other patient. With the exception of these patients, there was a general tendency for higher doses to result in better clinical responses, but there was not a clear dose-response relationship. Splenomegaly, tumor burden, and overall tumor size (bulk) seem to be important determinants of response, because patients with splenomegaly, large tumor burdens, and bulky adenopathy tended to respond less well to therapy than did patients without these attributes. There was a positive correlation between the intensity of imaging of known sites of disease with ^{111}In-anti-CD20 mAb and site-dependent tumor responses following therapy with ^{90}Y-anti-CD20 (data not shown), although some tumors that were visualized poorly responded well to therapy, and others that were well imaged failed to respond. Two of the patients who had CRs had involved BM prior to treatment, with negative marrow on biopsy after obtaining a radiographic CR. Fourteen of the 18 patients had better and/or longer responses to the RIT than they had had with their most recent previous courses of chemotherapy (including stable disease of longer duration). Eleven of the 18

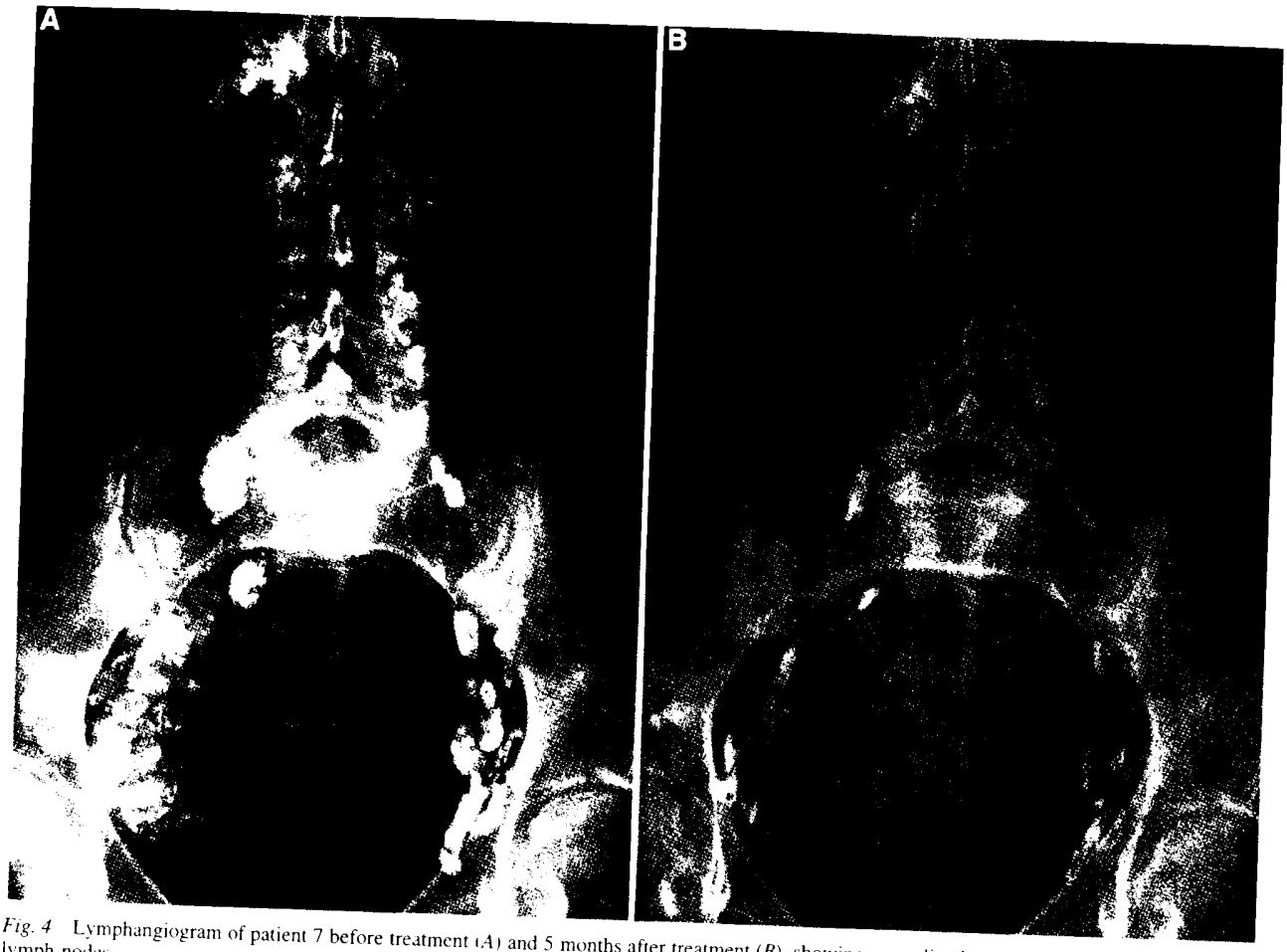

Fig. 4 Lymphangiogram of patient 7 before treatment (*A*) and 5 months after treatment (*B*), showing normalization of multiple previously enlarged lymph nodes.

patients had better responses (more tumor reduction) following RIT than they had had to prior chemotherapy. Examples of two of the observed clinical responses are shown in Figs. 4 and 5.

Responses of the retreated patients are summarized in Table 9. Two of the three patients retreated with ~40 mCi ^{90}Y-labeled antibody had subsequent PRs, and one is still ongoing at >12 months. One patient had no significant response to therapy, with PD 1.5 months following treatment. It is important to note that two of the three patients had larger tumor burdens prior to therapy the second time than they had had prior to the first treatment, and the patient who failed to respond to retreatment had bulky disease and circulating tumor cells at the time of retreatment.

DISCUSSION

RIT is a promising new therapeutic modality for the treatment of recurrent non-Hodgkin's lymphoma In the results reported here, RIT with ≤50 mCi ^{90}Y-anti-CD20 mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of ≤40 mCi ^{90}Y-anti-CD 20 mAb were nonmyeloablative. The preinfusion of unlabeled anti-CD20 mAb prior to administration of ^{111}In-anti-CD20 mAb resulted in improved antibody biodistribution primarily by decreasing splenic uptake and urinary excretion while increasing the relative uptake in disease sites. The results of the biodistribution studies reported here are consistent with those of other investigators and demonstrate that important determinants of antibody distribution include spleen size (26, 32), preinfusion or coinfusion of unlabeled antibody (12, 33), and tumor burden (12, 26). In this study, increasing doses of unlabeled anti-CD20 mAb resulted in the imaging of a higher proportion of known sites of disease, with visualization of 92% of the known sites of disease with 2.5 mg/kg unlabeled antibody. Preinfusion of unlabeled mAb also resulted in the imaging of occult sites of disease in several of the patients studied. The optimal dose of preinfused, unlabeled antibody, however, has yet to be determined. Differences in the ability of the two anti-CD20 antibodies (B1 and 2B8) to image known sites of disease are most likely due to the heterogeneity in the patient population in terms of spleen size, tumor burden, and tumor bulk. These patient characteristics are probably much more important determinants of anti-CD20 antibody biodistribution than inherent characteristics of the two anti-CD20 antibodies (*e.g.*, class and affinity) used; therefore, interpatient variability would mask any antibody-dependent differences in biodistribution following administration of equivalent doses of the two antibodies (B1 and 2B8; *e.g.*, 1 mg/kg). Other imaging

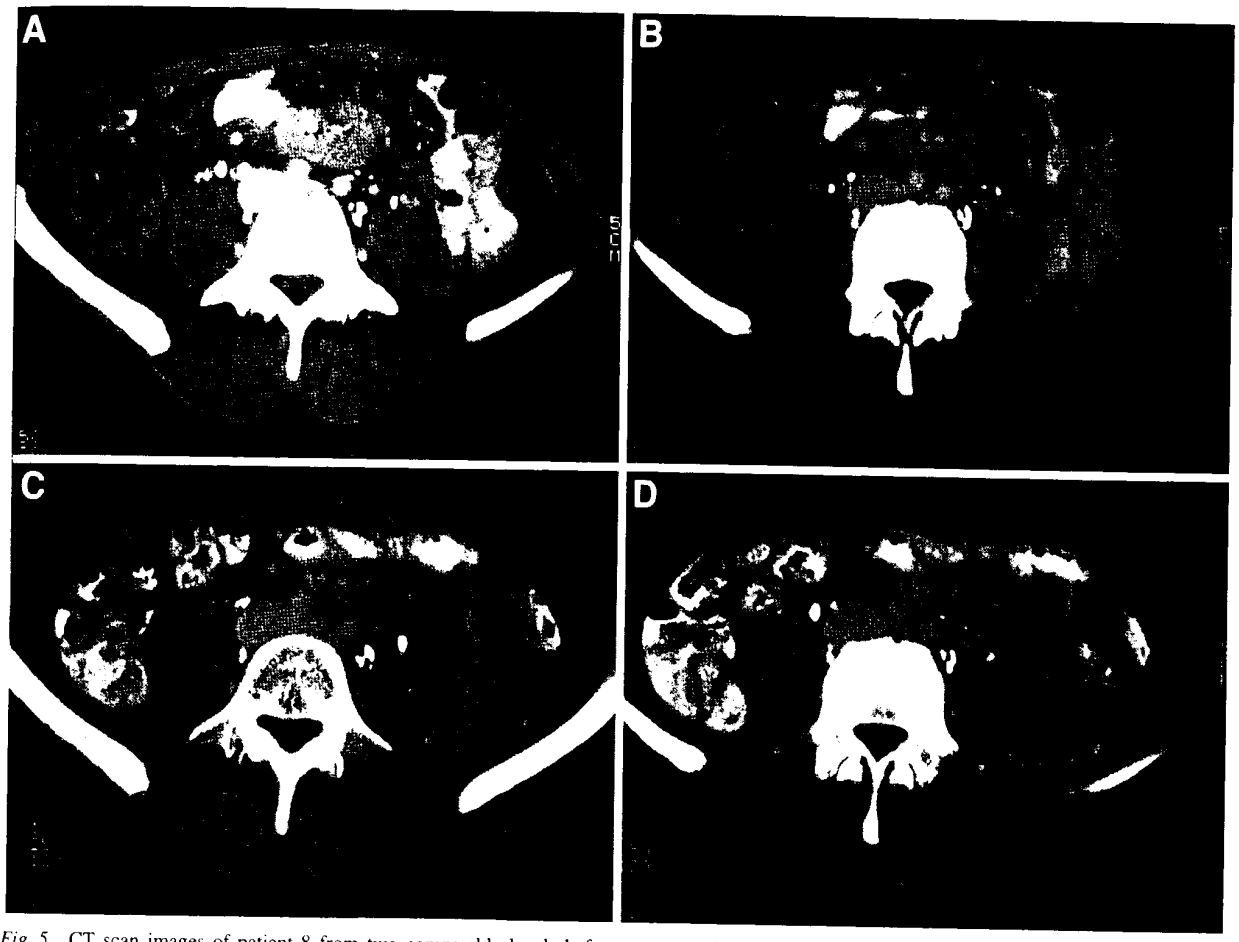

Fig. 5 CT scan images of patient 8 from two comparable levels before treatment (*A* and *B*) and 5 months after treatment (*C* and *D*), showing resolution of a large mesenteric mass.

Table 9 Clinical responses: retreated patients

Patient	Dose (m Ci)	Response	Pretreatment % tumor volume remaining (g)		Time to best response (months)	FFP (months)
6	42.9	PR	49	(52)	2	6.5
7	43.0	SD[a]	154	(250)		1.5
9	43.7	PR	38	(150)	5	15

[a] SD, stable disease.

studies in patients with hematological cancers have resulted in a rate of tumor visualization ranging from 72 to 100% (10, 11, 34) for disease sites larger than 2 cm (11). Improvements in biodistribution of radiolabeled antibody following preadministration of unlabeled antibody are presumably secondary, in part, to decreased, nonspecific uptake of intact antibody molecules by cells with Fc receptors within the reticuloendothelial system.

Antibody infusions were well tolerated, and nonhematological toxicity was minimal, with the exception of an infection rate of 22% (33% including fever and neutropenia with no sources) in patients following a single dose of ^{90}Y-anti-CD20 mAb. This rate of infection is lower than that of 47% reported for high doses of ^{131}I-labeled anti-CD20 mAbs (12) and is very similar to that observed following treatment with multiple doses of unlabeled, chimeric anti-CD20 (IDEC-C2B8) mAb (10 of 47 patients with any grade infection during or up to 1 month after treatment) (48).

Myelotoxicity was dose limiting, and at the 50-mCi dose level, all four patients had grade 4 hematological toxicity, and two patients required PSC reinfusion. Important determinants of toxicity included dose and BM reserve (prior cytotoxic therapy). One of the eligibility criteria for study entry was that patients

have <25% BM involvement at the time of BM harvest or PSC collection. Most patients with recurrent lymphoma have more extensive BM involvement and cannot meet this eligibility criterion. Because half (9 of 18) of the patients studied had negative BM biopsies prior to therapy, it is difficult to comment on the relationship between the extent of BM involvement and subsequent myelotoxicity. Given the limited extent of BM involvement in this selected patient population, BM involvement did not seem to affect the subsequent grade of hematological toxicity. Obviously, this observation is limited by the relatively small patient numbers and the low level of BM involvement in the patients studied. In the one patient we treated with 34% of circulating tumor cells at the time of retreatment, localization of radiolabeled antibody in the marrow contributed presumably to her subsequent need for PSC reinfusion.

Important determinants of efficacy included dose, tumor burden and bulk, and spleen size. The overall response rate in this Phase I/II study was 72%, with FFPs of 3–29+ months. The response rate for patients treated with nonmyeloablative doses of ≤40 mCi was 78%. This is promising, considering the relatively unfavorable antibody biodistributions that were obtained in some of the patients. Unlike patients treated in other studies (12), a favorable biodistribution based on predicted tumor dosimetry or splenic update was not required prior to therapy with ^{90}Y-anti-CD20 mAb. Nevertheless, two patients with massive splenomegaly had PRs, and 7 of 10 patients with bulky disease ≥5 cm in diameter had significant clinical responses (5 PRs and 2 CRs). These results compare favorably with results of other nonmyeloablative RIT studies in patients with recurrent B-cell lymphoma in which response rates have ranged from 5 to 78% (mean, 58%; Ref. 9). Admittedly, it is difficult to make direct comparisons from one study to another, given that these studies have differed considerably in study design, eligibility criteria, antibody and radionuclides used, antibody and radionuclide doses, number of treatments, labeling methods, doses of unlabeled antibody preinfused or coinfused, and the biodistribution or dosimetry estimations required for administration of a therapeutic dose of radiolabeled antibody (9).

It is interesting that, although higher doses of RIT have tended to be more efficacious, there has not been a direct correlation between tumor dosimetry and response in most reported studies (9). Clearly, dose is only one of several determinants of efficacy, which include antibody specificity, characteristics of the targeted antigen, immunoconjugate stability, and the other factors listed above. The relatively high response rate reported here with a number of durable PRs and CRs is encouraging in this relatively unfavorable patient population. Although caution should be exerted in the interpretation of these results, given the relatively small numbers of patients, limited follow-up, and predominance of patients with low-grade lymphoma treated in this study, many patients have had remissions of longer durations than achieved with previous chemotherapy. These responses have been obtained with relatively low tumor doses, most of which are considerably lower than doses usually required to achieve similar responses using conventional fractionated, high-dose rate, external beam radiation therapy. Other investigators have reported similar, surprisingly good clinical responses with low doses of administered radiolabeled mAbs (10, 35–37) and low tumor doses (22). The apparent increased relative efficacy of RIT compared with equivalent doses of high-dose rate, external beam radiation therapy is probably secondary to a number of factors, including an inverse dose rate effect and radiation- and antibody-induced apoptosis (9, 38).

Although fractionated RIT has been reported to be less toxic and more efficacious than single doses of RIT (39–43), the results of retreatment in this study were somewhat disappointing. Two of the three patients retreated with ~40 mCi ^{90}Y-labeled antibody had PRs, but the overall response rate was lower than that observed in patients following single doses of ^{90}Y-mAb, and toxicity was considerably greater. The decreased efficacy and increased toxicity in the retreatment group are probably secondary to their overall unfavorable status at the time of retreatment, with two of the three patients having more extensive and bulkier disease than they had prior to initial therapy and one of the three patients having extensive BM involvement at the time of retreatment.

It is possible that fractionated therapy with retreatment of patients when they are in a relatively minimal disease state with a stabilized minor response or PR may be more efficacious and better tolerated. Selection of patients with a favorable biodistribution as well as the use of higher doses of unlabeled antibody (*e.g.*, 2.5 mg/kg) may increase the efficacy of this therapy further. A variety of approaches are being investigated to increase the therapeutic efficacy and decrease the toxicity of RIT (38, 44–47). Application of advances in the field may increase further the therapeutic index of this promising new therapeutic modality for the treatment of patients with recurrent non-Hodgkin's lymphoma.

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CLINICAL TRIALS

REFERRAL RESOURCE

COMPILED BY
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NATIONAL CANCER INSTITUTE

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it also will enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered in clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically *not* soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients not in a study.

This month's installment of Clinical Trials Referral Resource is devoted to studies of the anti-CD20 monoclonal antibody rituximab (Rituxan).

For patient entry information, see the individual trials.

* PDQ is a comprehensive database service provided by the National Cancer Institute's International Cancer Information Center and Office of Cancer Communications for retrieval of cancer treatment information, including peer-reviewed statements on treatment options, supportive care, screening, and prevention; and an international clinical trials registry. For more information on PDQ, Internet access is available at http://cancernet.nci.nih.gov/pdq.htm, or contact the Cancer Information Service offices (1-800-4-CANCER).

Current Clinical Trials of the Anti-CD20 Monoclonal Antibody Rituximab

Rituximab (Rituxan) was the first monoclonal antibody approved by the FDA for the therapy of a malignant disease. The approval of this drug provided validation for monoclonal antibodies and target-specific therapies in the treatment of cancer.

As a single agent, rituximab has a very good tolerability profile and significant efficacy against follicular B-cell lymphomas.[1] The toxicities that result from rituximab infusion are generally not overlapping those of other therapeutic modalities, making rituximab compatible with other established therapies given at standard doses. Additionally, there is a broad assortment of B-cell malignancies that express the target antigen (CD20) so that the full utility of rituximab is only now being explored.

Rituximab is a chimeric (mouse-human) monoclonal antibody that binds to CD20, a pan B-cell antigen that appears to play a role in activation and proliferation of normal B cells.[2,3] Binding of the antibody to CD20-bearing cells can induce both complement-mediated cytolysis and antibody-dependent cellular cytotoxicity, and can also directly induce apoptosis in malignant cell lines.

Intravenous administration of the antibody into nonhuman primates leads to depletion of circulating B cells.[4] Clinical trials in patients with relapsed indolent non-Hodgkin's lymphoma (NHL) have shown that the antibody can induce significant regressions in approximately half of all treated patients, with a median time to disease progression exceeding 13 months.[1]

The primary toxicities are related to the initial infusion and represent a cytokine-release syndrome characterized by flu-like symptoms including fever, chills, hypotension, and rarely, bronchospasm. Initial concern that the B-cell depletion associated with rituximab may be immunosuppressive has not been realized in clinical experience.

Treatment with rituximab can induce short regressions in patients with relapsed aggressive histology CD20-positive NHL, but benefit is limited for these patients.[5] However, preliminary phase II studies administering combinations of rituximab with CHOP chemotherapy (cyclophosphamide [Cytoxan, Neosar], doxorubicin HCl, vincristine [Oncovin], and prednisone) appear to be able to induce prolonged remissions in patients with both indolent and aggressive disease.[6,7]

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CLINICAL TRIALS

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There are still many unknowns concerning the appropriate use of rituximab in the therapy of CD20-positive diseases. For this reason, an extensive clinical evaluation is under way, with a plethora of trials. All stages of clinical trials are ongoing addressing the following questions:

- Which of the possible mechanisms are predominant in the efficacy of the antibody, and how can they be augmented?
- Will increased doses improve therapeutic effects? Can recurrent or maintenance therapy prolong remission? Can rituximab be given intrathecally?
- What is rituximab's role in the therapy of other B-cell malignancies, including human immunodeficiency virus or immunosuppression-related NHL, Hodgkin's disease, Waldenström's macroglobulinemia, mantle cell and Burkitt's lymphomas, acute and chronic lymphocytic leukemias, hairy cell leukemia, multiple myeloma, and nonmalignant autoimmune diseases?
- What is rituximab's role in primary therapy, for both limited- and advanced-stage disease? Is the antibody more effective when used for limited disease bulk, or should the traditional watch and wait approach be maintained?
- Are therapeutic combinations going to provide superior outcomes? Can rituximab be used with different chemotherapy regimens and/or radiation (including combination with all accepted chemotherapy regimens) or immune stimulatory cytokines (GM-CSF [sargramostim, Leukine], vaccines, and interleukins 2 and 12)?

The results of these clinical trials should be available within the next 5 years. It is quite likely that rituximab will significantly impact the prognosis for B cell NHL and perhaps even other diseases. The following list includes a selection of approved/active studies with rituximab that are being sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, or by the pharmaceutical sponsors.

Lymphoma

1

- **Title**—Dose-Adjusted EPOCH Chemotherapy and Rituximab (CD20+) in Previously Untreated Aggressive Non-Hodgkin's Lymphoma
- **Protocol Number**—T93-0023
- **Participating Institutions**—National Cancer Institute Medicine Branch, Biological Response Modifiers Program, Massachusetts General Hospital, University of Maryland Cancer Center
- **Contact**—Wyndham H. Wilson, MD, (301) 435-2415

2

- **Title**—EPOCH Chemotherapy +/- IL-12 for Previously Untreated and EPOCH plus Rituximab for Previously Treated Patients With AIDS-Associated Lymphoma
- **Protocol Number**—T96-0036
- **Participating Institutions**—National Cancer Institute Medicine Branch
- **Contact**—Wyndham H. Wilson, MD, (301) 435-2415

3

- **Title**—Phase III Trial of CHOP vs CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Older Patients with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large-Cell Histology Non-Hodgkin's Lymphoma
- **Protocol Number**—E4494
- **Participating Groups**—Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, Southwest Oncology Group
- **Contact**—Jean MacDonald, (617) 632-3610

4

- **Title**—Randomized Trial of CHOP Chemotherapy with or without Rituximab (Chimeric Anti-CD20 Antibody) for HIV-Associated Non-Hodgkin's Lymphoma
- **Protocol Number**—AMC-010
- **Participating Institutions**—AIDS-Associated Malignancies Clinical Trials Consortium, University of California at Los Angeles, University of Southern California, Georgetown University Hospital, University of Miami, Northwestern University, Massachusetts General Hospital, Duke University Medical Center, New York University Medical Center, Memorial Sloan-Kettering Cancer Center, Mount Sinai Medical Center, Roswell Park Memorial Institute
- **Contact**—Lawrence D. Kaplan, MD, (415) 476-4082

5

- **Title**—A Phase II Trial of C2B8 in Patients with Asymptomatic CD20+ B-Cell Follicular Small Cleaved Low-Grade Non-Hodgkin's Lymphoma or Relapsed CD20+ Hodgkin's Disease
- **Protocol Number**—NCCTG-98-78-51
- **Participating Groups/Institutions**—North Central Cancer Treatment Group, Mayo Clinic
- **Contact**—Thomas E. Witzig, MD, (507) 284-0527

6

- Title—Phase I Study of Interleukin-12 in Combination With Rituximab in patients with Non-Hodgkin's Lymphoma
- **Protocol Number**—T99-0052
- **Participating Institutions**—Mayo Clinic
- **Contact**—Stephen M. Ansell, MD, PhD, (507) 284-0923

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CLINICAL TRIALS

Continued from page 1440.

7

- **Title**—Evaluation of CHOP Plus Rituximab Plus Involved Field Radiotherapy for Stages I, IE and Non-Bulky Stages II and IIE, CD20 Positive, High-Risk Localized Aggressive Histologies of Non-Hodgkin's Lymphoma
- **Protocol Number**—S0014
- **Participating Group**—Southwest Oncology Group
- **Contact**—Marj Godfrey, (210) 677-8808

8

- **Title**—Pilot Study of Idiotype Vaccine and EPOCH-Rituximab Chemotherapy in Untreated Mantle Cell Lymphoma
- **Protocol Number**—1033
- **Participating Institutions**—National Cancer Institute Medicine Branch
- **Contact**—Wyndham H. Wilson, MD, (301) 435-2415

9

- **Title**—Phase III Randomized Trial of CHOP Plus Rituxan vs CHOP Alone for Newly Diagnosed, Previously Untreated, Aggressive Non-Hodgkin's Lymphoma (NHL)
- **Protocol Number**—U0795s
- **Participating Institution**—University of Nebraska
- **Contact**—Julie M. Vose, MD, (402) 559-3848

10

- **Title**—Phase II Pilot Study of the Safety and Efficacy of Rituxan in Combination With Fludarabine Chemotherapy in Patients with Low-Grade or Follicular Lymphoma
- **Protocol Number**—U0791n
- **Participating Institution**—Roswell Park Cancer Institute
- **Contact**—Myron S. Cruczman, MD, (716) 845-7695

11

- **Title**—Phase II Trial of Rituximab With Short Duration Chemotherapy as Initial Treatment for Low-Grade Follicular NHL
- **Protocol Number**—U2094n
- **Participating Institution**—Sarah Cannon Cancer Center
- **Contact**—John D. Hainsworth, MD, (615) 342-1725

12

- **Title**—Fludarabine, Mitoxantrone and Dexamethasone (FND) Plus Chimeric Anti-CD-20 Monoclonal Antibody (IDEX-C2B8) for Stage IV Indolent Lymphoma (DM97-261)
- **Protocol Number**—U0794n
- **Participating Institution**—M. D. Anderson Cancer Center
- **Contact**—Peter McLaughlin, MD, (713) 792-2860

13

- **Title**—Rituximab Plus GM-CSF in Patients With Relapsed Low Grade or Follicular B-Cell Lymphoma (DM98-304)
- **Protocol Number**—U2018n
- **Participating Institution**—M. D. Anderson Cancer Center
- **Contact**—Peter McLaughlin, MD, (713) 792-2860

14

- **Title**—Rituximab Induction Therapy Followed by Randomization of Responders to Maintenance Therapy With Rituximab vs Treatment with Rituximab at the Time of Progression in Patients With Previously Treated Low-Grade Non-Hodgkin's Lymphoma
- **Protocol Number**—U0837n
- **Participating Institution**—Sarah Cannon Cancer Center
- **Contact**—John D. Hainsworth, MD, (615) 342-1725

15

- **Title**—Treatment of Low-Grade and Mantle Cell Lymphoma With High-Dose Therapy and Stem Cell Support Followed by Consolidative Immunotherapy with Rituximab
- **Protocol Number**—U0798s
- **Participating Institutions**—Toronto-Sunnybrook Regional Cancer Center
- **Contact**—Neil Berinstein, MD, (416) 480-6100

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16

- **Title**—Clinical Trial of C2B8 Monoclonal Antibody Following High Dose Therapy and Autografting in B-Cell Non-Hodgkin's Lymphoma
- **Protocol Number**—U0768s
- **Participating Institutions**—Stanford University
- **Contact**—Sandra J. Horning, MD, (650) 725-6456

17

- **Title**—Phase II Trial of Rituxan and BEAM High-Dose Chemotherapy and Autologous Peripheral Blood Progenitor Transplant for Indolent Lymphoma
- **Protocol Number**—U2234n
- **Participating Institutions**—University of Nebraska
- **Contact**—Julie M. Vose, MD, (402) 559-3848

18

- **Title**—Phase II Trial to Evaluate the Efficacy of Rituxan in Patients With Lymphocyte Predominant Hodgkin's Disease
- **Protocol Number**—U2082n
- **Participating Institutions**—Stanford University
- **Contact**—Sandra J. Horning, MD, (650) 725-6456

Lymphoproliferative Disorder

1

- **Title**—Phase II Study of Peripheral Blood Stem Cell Transplant and Immunotherapy for Patients With Lymphoproliferative Disorders
- **Protocol Number**—U1133n
- **Participating Institutions**—Johns Hopkins Oncology Center
- **Contact**—Ian W. Flinn, MD, (410) 614-4557

Multiple Myeloma

1

- **Title**—Phase II Study of the Anti-CD20 Monoclonal Antibody Rituxan in Multiple Myeloma
- **Protocol Number**—U0805n
- **Participating Institution**—Dana-Farber Cancer Institute
- **Contact**—Steven P. Treon, MD, PhD, (617) 632-2144

Waldenström's Macroglobulinemia

1

- **Title**—Rituximab for Waldenström's Macroglobulinemia (WM): A Phase II Pilot Study for Untreated and Previously Treated Patients
- **Protocol Number**—E3A98
- **Participating Group**—Eastern Cooperative Oncology Group
- **Contact**—Jean MacDonald (617) 632-3610

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Treatment Outcome and Prognostic Factors for Primary Mediastinal (Thymic) B-Cell Lymphoma: A Multicenter Study of 106 Patients

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Purpose: **To define clinicopathologic features, response to treatment, and prognostic factors of primary mediastinal B-cell lymphoma (MBL), a CD20+ tumor recognized as a distinct entity among non-Hodgkin's lymphomas (NHL).**

Patients and Methods: **One hundred six patients presented with disease confined to thorax (86%), bulky mediastinum (73%), superior vena cava syndrome (47%), and contiguous infiltration (57%). Ninety-nine received doxorubicin-containing chemotherapy (CHT).**

Results: **Thirty-five of 99 patients were primarily CHT-resistant, and 64 responded: 23 achieved complete response (CR) and 41 achieved response with residual mediastinal abnormality. Seventy-seven percent of responders received mediastinal radiotherapy (RT). Of 64 responders, 18 (28%) relapsed: none of 23 CR patients and 18 of 41 (44%) with residual mediastinal abnormality. Relapse-free survival rate of responders was 71% at 3 years. Actuarial 3-year survival rate was 52% for all patients and 82% for responders. Predictive factors of poor outcome were identified by logistic regression; Cox survival analysis was performed on death and relapse. Pericardial effusion ($P < .001$) and Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 ($P = .009$) predicted nonresponse (NR) and affected survival. Less than partial midway response to CHT predicted NR to subsequent therapies. Bulky disease was related to persistent mediastinal abnormality and risk of relapse ($P = .025$).**

Conclusion: **MBL is an aggressive NHL with unique clinicopathologic aspects, often refractory to current CHT designed for high-grade NHL. Poor performance status and pericardial effusion predict NR and poor survival. Inadequate response after the first courses of front-line CHT predicts failure of subsequent treatment. Responders with bulky mediastinum or residual mediastinal abnormality after CHT are at risk of relapse. These factors should help to select high-risk patients for intensive treatments.**

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PRIMARY B-CELL lymphoma of the mediastinum has a relatively recent history. The first clinical and pathologic descriptions appeared in the early 1980s.[1-3] In the mid-1980s it was recognized as a distinct clinicopathologic entity and the B-cell phenotype of the tumor was established.[4-6] In 1994, it was included in the Revised European-American Lymphoma (REAL) classification as primary mediastinal (thymic) large B-cell lymphoma (MBL).[7] The many reports on MBL describe this entity as a non-Hodgkin's lymphoma (NHL) occurring in young adults, prevalently women, with symptoms of a rapidly enlarging mass of the upper anterior mediastinum, with frequent superior vena cava compression. The tumor is usually bulky and often invades contiguous thoracic structures (lung, pleura, pericardium, chest wall), while extrathoracic spread is uncommon at diagnosis. At relapse or progression, extrathoracic diffusion tends to involve unusual sites such as kidney, breast, adrenal cortex, and ovaries.[8-15] Morphologically, the lymphoma is composed of medium-sized to very large cells, with clear cells and sclerosis of variable intensity as characteristic features.[5,6,16] The cells show a B-cell SIg-negative phenotype CD10−, CD19+, CD20+, CD21 −, and CD22+.[6,17-19] It has been suggested that this tumor may originate from a specific population of B cells resident in the thymus (thymic B-cell lymphoma).[10,20-24]

Although the characteristic clinical features of MBL have been described often, because of the relatively low frequency of this lymphoma, few reports deal with prognostic factors. It appears from many studies that intensive chemotherapy (CHT), usually followed by consolidation radiotherapy (RT), may result in long-term disease-free survival and possibly cure in a good proportion of patients.[8,11,13-15,23,25-27] However, in a substantial minority, the disease is highly refractory to first- and second-line therapy, with a uniformly fatal outcome. These poor-risk patients constitute approximately 50% of cases in some series.[13-15] Early identification of poor-risk patients who cannot achieve long-term disease-free survival with current treatments would help to assign these cases to innovative therapies from the onset. We report the results of

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a multicenter retrospective study on treatment outcome and prognostic factors of a series of 106 adults with MBL treated at four European centers.

PATIENTS AND METHODS

This study includes 106 consecutively observed adult patients with primary MBL diagnosed from 1984 to 1995 at four European hospitals. All patients presented with a mass in the upper anterior mediastinum, either isolated or with direct extension to contiguous lymph nodes (hilar, supraclavicular) or to adjacent intrathoracic structures.

Pathology

Diagnostic tissue was obtained by thoracotomy, mediastinotomy, mediastinoscopy, or needle biopsy in 87 cases, and in 19 from lymph nodes in the supraclavicular fossa that were direct extensions of the mediastinal tumor. From each tumor tissue specimen, routine stains, including hematoxylin-eosin and Giemsa, were newly performed together with a CD20(L26) immunostaining demonstrating the B-cell nature of the tumor, which was prerequisite. The histologic sections were examined by four of us (M.P., J.S., U.G., and P.M.). Three categories were defined to reflect the cell size (I, medium-sized cells, 3%; II, large, 79%; III, very large, 18%). Presence (B type, 18%) versus absence (A type, 82%) of prominent nucleoli and immunoblast-like morphology were additional discriminators. Prominent histologic features such as presence versus absence of major degrees of sclerosis and presence versus absence of necroses were also evaluated.

Staging

All patients were staged clinically, with history, physical examination, routine laboratory tests, bone marrow biopsies, plain chest x-rays (CXR), and chest computed tomographic (CT) scan. Abdominal CT scan was performed in 97 patients and abdominal sonography in nine. The mediastinal mass was defined as bulky if it was $\geq$ 10 cm in diameter on posteroanterior chest film.

Treatment

Of 106 patients, three died pretherapy from massive lung, pleuropericardial, myocardial, and caval infiltration; two had RT only; two received palliation CHT because of advanced age and associated illness; and 99 are assessable for response to CHT. CHT consisted of combination doxorubicin-containing regimens: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in 36 patients; methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) or etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B) in 29; CHOP with doxorubicin repeated on day 2 (CH2OP) in 11; CHOP plus etoposide 100 mg/m^2 on days 1 to 3 (CHOEP) in 10; CHOP with cyclophosphamide 1,200 mg/m^2 on day 1 (hCHOP)/ifosfamide, vindesine, etoposide, and prednisone (IVEP) or CHOP/etoposide, ifosfamide, methotrexate and prednisone(VIM) in 13. Consolidation mediastinal RT was administered to 77% of responders. Median follow-up duration was 50 months (range, 16 to 135).

Evaluation of Response

Response was evaluated using plain CXR and chest CT scan. Complete response (CR) was defined as disappearance of all clinical evidence of disease, with normalization of laboratory values and return to normal of radiographic findings. Partial response (PR) was defined as a decrease by at least 50% in the sum of the products of the largest perpendicular diameters of the mediastinal tumor. A residual mediastinal mass of uncertain significance was frequently detected by posttreatment CT scan. On the other hand, residual radiographic abnormalities in lymphoma do not necessarily imply active disease. Therefore, in this study, patients with residual mediastinal masses with no other evidence of disease were considered together with CRs for the analysis of factors affecting response and survival. Nonresponse (NR) was defined as a less than 50% decrease in the tumor mass, or tumor growth during therapy. Because few patients had a gallium 67 (^{67}Ga) scan, this technique was not used to assess response.

Statistical Analysis

The following features were evaluated for prognostic value: age, sex, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale of 0 to 4, B symptoms, Ann Arbor stage, bulkiness of mediastinal tumor, number of extranodal sites of involvement, presence of superior vena cava syndrome (SVCS), presence of pleural or pericardial effusion, erythrocyte sedimentation rate, serum lactate dehydrogenase (LDH) level, serum albumin level, pathologic categories, type of response to CHT (CR v response with residual mass), risk group defined by the International Prognostic Index (IPI),[28] and relative dose-intensity (RDI) of doxorubicin and cyclophosphamide. Actual dose-intensity (ADI) for each drug was calculated according to Hryniuk and Bush[29] and was expressed as milligrams per square meter per week; the RDI was computed as the percent of dose-intensity corresponding to protocol doses and schedule (RDI = ADI $\times$ 100/protocol dose-intensity). Data on pretreatment serum β2-microglobulin (β2-M) levels were available for a minority of cases (19%); therefore, this serum marker was not included in the analysis. Clinical and pathologic factors that influenced response to front-line CHT were identified by logistic regression: univariate odds ratios (OR) were calculated, together with their 95% confidence intervals (CI); factors significant at a .1 level were included in a multivariate model; features independently associated with response were selected with the stepwise procedure. Survival was calculated from the date of diagnosis to the date of death or of the last follow-up evaluation. Relapse-free survival for responders was calculated as the interval between the end of CHT and relapse or death or the date of last follow-up evaluation. Survival curves were plotted by the method of Kaplan and Meier. Score test (log-rank test) was used to identify univariate predictors; multivariate Cox regression analysis was performed to identify prognostic characteristics associated with overall and relapse-free survival; factors significant at a .1 level at univariate analysis were included in the model and were selected by stepwise procedure. Hazards ratios (HR) and their 95% CIs were computed. EGRET (SERC, Seattle, WA) and Statistica 5.0 (Statsoft, Tulsa, OK) packages were used for computation.

RESULTS

Clinical Features

Table 1 lists patient characteristics at presentation. Median age was 30 years. There were 49 men and 57 women. Of 106 patients, 100 (94%) presented with chest symptoms due to a mediastinal mass. The median time from

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Table 1. Patient Characteristics (N = 106)

	No of Patients	%
Median age, years	30	
Range	14-73	
Sex		
Male	49	46
Female	57	54
Performance status ≥ 2	29	27
B symptoms	31	29
Symptoms of mediastinal mass	100	94
Median duration of symptoms (days)	48	
Range	14-152	
SVCS	50	47
Bulky mediastinum (≥ 10 cm)	78	73
Pleural effusion	38	36
Pericardial effusion	27	25
Infiltration of contiguous thoracic structures	60	57
Extrathoracic localization at diagnosis	11	10
LDH > 1 × normal	55	52

onset of symptoms to diagnosis was 56 days. B symptoms were present in 31 patients (29%). Clinical symptoms of SVCS were present at diagnosis in 50 patients (47%), and 14 others (13%) showed subclinical superior caval compression on CT scan, for an overall incidence of caval obstruction of 60%. Tracheo-bronchial compression or dislocation was revealed by CT scans and/or bronchoscopy in 41 patients (39%). The mediastinal mass was bulky in 78 patients (73%). Pleural effusion was found in 38 patients (36%), and pericardial effusion in 27 (25%). In 60 patients (57%), staging procedures documented extension to extranodal intrathoracic sites adjacent to the mediastinal mass (lung parenchyma in 35, pleura in 25, chest wall in 17, pericardium in 27, myocardium in three, vena cava in nine, innominate vein in two, arteria pulmunaris in two). In three patients, CT scan showed caval infiltration with severe obstruction and thrombosis. Fifteen patients (14%) had extrathoracic localizations at diagnosis: paraortic lymph nodes in eight, bilateral kidney infiltration in five, and infiltration of pancreas, stomach, bilateral breast in one each. No patient showed splenomegaly or spleen abnormalities on CT or sonographic abdominal examination. Bone marrow biopsies were negative in all patients except one. Serum LDH levels were elevated (> 460 mU/mL) in 55 patients (52%). Serum β2-M levels were available for 20 patients and were in the normal range in all cases.

After clinical staging, 18 patients showed extension to one contiguous extranodal site, while 31 had more than one contiguous site of extension in the thorax. Because of the frequent and extensive involvement of contiguous intrathoracic structures, classification of MBL patients by the standard Ann Arbor system as stage IIE or IV based solely on the number of contiguous sites involved may result in arbitrary assignment to localized or advanced disease. Therefore, we coded the stage of our patients in the following two ways: (1) considering patients with contiguous intrathoracic extension as stage IIE independently of the number of sites involved, 19 (18%) were stage I, 23 (22%) stage II, 49 (46%) stage IIE, five (5%) stage III, and 10 (9%) stage IV; (2) considering the 31 patients with more than one contiguous site of extension as stage IV, the resulting breakdown was 19 patients (18%) stage I, 23 (22%) stage II, 18 (17%) stage IIE, five (5%) stage III, and 41 (38%) stage IV.

Response to Treatment

Of 99 patients assessable for response to CHT, 35 (35%) showed primary resistance to treatment, and 64 (65%) responded: 23 achieved a CR and 41 a response with residual mediastinal abnormality. The type of response was related to bulky status at presentation. Persistent residual mediastinal mass was observed in five of 18 responders (28%) who presented with nonbulky disease versus 36 of 46 (78%) who presented with bulky mediastinum (P = .0003). Of 64 responders to first-line CHT, 49 (77%) received consolidation RT to the mediastinum at doses ranging from 36 to 44 Gy. RT was given to 17 of 23 patients (74%) in CR and to 32 of 41 (78%) with residual mediastinal abnormality.

Of the 35 NRs, 31 showed early resistance to first-line CHT with either less than a PR or progression of mediastinal tumor at CXR performed 6 to 9 weeks after starting treatment. The other four showed PR midway through CHT but worsened by the end of the scheduled therapy. Salvage treatments included radiation therapy in 20, high-dose cytarabine with or without mitoxantrone in 11, high-dose cyclophosphamide in two, etoposide with cytarabine in three, and high-dose CHT plus autologous progenitor cell transplantation (APCT) in three, but none responded.

Survival

Fifty-two patients were alive at the last update, with a median follow-up of 50 months (range, 16 to 135). The actuarial 3-year survival rate was 50% for the entire series of 106 patients (Fig 1), 52% for the 99 patients assessable for CHT, and 82% for responders. The median survival of NRs was 10 months, none surviving more than 32 months (Fig 2).

Relapse

Of 64 responders, 18 (28%) relapsed after a median response duration of 6 months (range, 3 to 34). The re-

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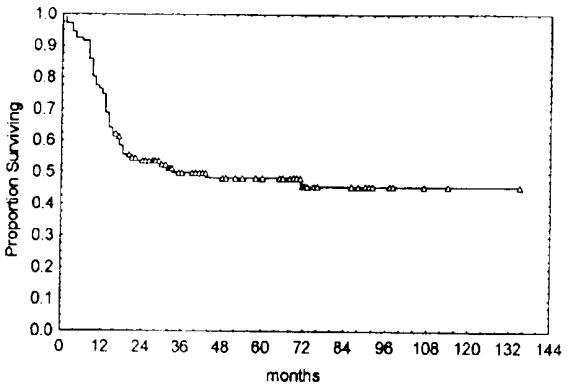

Fig 1. Overall survival of 106 patients with primary MBL.

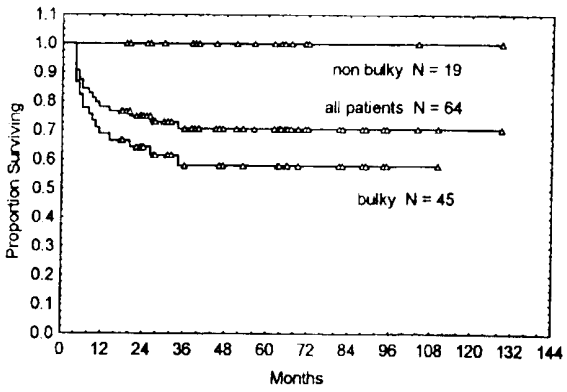

Fig 3. Relapse-free survival of 64 responders to CHT in relation to the presence of bulky mediastinum at diagnosis.

lapse-free survival rate of responders was 71% at 3 years (Fig 3). The relapse rate was 24.5% (12 of 49) for patients who received postchemotherapy RT and 40% (six of 15) for patients who did not (P = .32). Of relapsing patients, 13 had exclusively intrathoracic progression, one had progression only in the abdomen, and four had both thoracic and extrathoracic spread (abdominal nodes in four; liver in three; kidney in one; stomach in one; breast in one). Mediastinal RT did not influence the pattern of recurrence, because 11 of 12 relapses that occurred in patients who received RT and six of six in non-RT patients were intrathoracic. The median interval to recurrence was 8.5 months (range, 3 to 19) and 6.5 months (range, 3 to 33), respectively. Treatment of relapse included RT plus CHT in four, high-dose cytarabine plus mitoxantrone in five, high-dose CHT with APCT in six, high-dose cyclophosphamide in one, various CHT in five, and no CHT in one. Median survival duration from relapse was 7 months. Five patients, all treated with high-dose CHT plus APCT, are alive: two in CR after 9 and 75 months, two with residual mediastinal abnormalities after 7 and 51 months, respectively, and one with active disease.

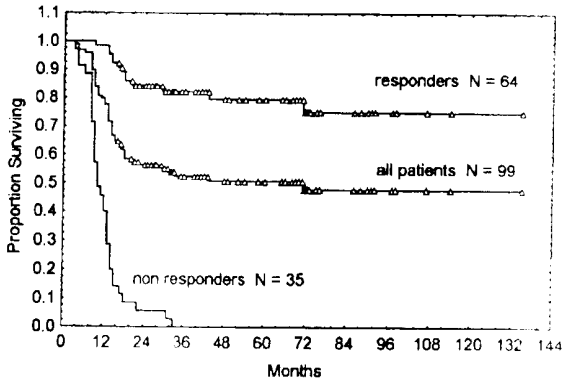

Fig 2. Survival curves of 99 patients with primary MBL according to response to front-line therapy.

Prognostic Factors for NR, Survival, and Relapse

The characteristics significantly predicting NR to front-line CHT at univariate analysis were as follows (Table 2): performance status ≥ 2; pericardial effusion; serum LDH level greater than normal; and an RDI of doxorubicin and cyclophosphamide less than 80%. In multivariate analysis, the two most important independent factors selected by stepwise logistic regression were poor performance status and pericardial effusion.

The following characteristics showed significant univariate association with risk of death: poor performance status, pericardial effusion, high serum LDH level, and bulky mediastinum. Multivariate stepwise Cox regression

Table 2. Risk Factors for Nonresponse to Front-Line CHT

Characteristic	OR	95% CI	P
Univariate analysis			
Performance status			
≥ 2 v 0 or 1	4.2	1.6-12.5	.002
Pericardial effusion			
Yes v no	3.0	1.1-8.3	.015
Serum LDH level			
> 1 × normal v ≤ 1 × normal	1.6	1.04-2.6	.034
RDI of doxorubicin and cyclophosphamide			
< 80% v ≥ 80%	3.2	1.1-10	.038
Multivariate analysis			
(stepwise logistic regression)			
Performance status			
≥ 2 v 0 or 1	3.5	1.4-8.6	.009
Pericardial effusion			
Yes v no	2.9	1.6-5.2	< .001

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analysis selected a poor performance status and pericardial effusion at diagnosis as the two main independent factors associated with risk of death (Table 3). In fact, as the response to first-line CHT is the major determinant of survival, the factors influencing response to CHT also affect survival.

Bulky mediastinum among presenting features and the persistence of residual mediastinal mass at the end of CHT were the only significant predictors of relapse at univariate analysis. None of 19 responders with nonbulky mediastinum relapsed, versus 18 of 45 responders (40%) who had bulky tumor (P = .0006). Figure 3 shows the relapse-free survival of 64 responders to CHT according to the presence of bulky mediastinum at diagnosis. Regarding the type of response to CHT, none of 23 CRs relapsed, versus 18 of 41 responders (44%) with residual mediastinal abnormality (P = .0001). Multivariate stepwise Cox regression analysis selected as independent prognostic variable for relapse-free survival bulky mediastinum or, alternatively, residual radiographic mediastinal abnormality after CHT. Two separate models were fitted because of the multicollinearity of the two variables (Table 4). The following histomorphologic criteria had no prognostic relevance: cell size, cytologic appearance of tumor cells, and presence versus absence of sclerosis and necroses.

The prognostic value of the age-adjusted IPI was investigated in 96 patients of our series, age ≤ 60 years. To avoid possible bias in the predictivity of the model as a result of disease classification by the standard Ann Arbor system as localized (stage IIE) or advanced (stage IV) only according to the presence of one or more than one site of contiguous extranodal extension in the thorax, we calculated the IPI score by two alternative modalities:

Table 3. Prognosis Factors for Survival

Characteristic	HR	95% CI	P
Univariate analysis (score test)			
Performance status			
≥ 2 v 0 or 1			< .001
Pericardial effusion			
Yes v no			.001
Serum LDH level			
> 1 × normal v ≤ 1 × normal			.010
Bulky mediastinum			
Yes v no			.020
Multivariate analysis (Cox stepwise regression)			
Performance status			
≥ 2 v 0 or 1	2.7	1.5-4.8	< .001
Pericardial effusion			
Yes v no	2.4	1.4-4.3	.002

Table 4. Risk Factors for Relapse

Characteristic	HR	95% CI	P
Univariate analysis (score test)			
Bulky mediastinum			
Yes v no			.006
Residual mediastinal abnormality			
Yes v no			.001
Multivariate analysis (Cox stepwise regression)			
Model 1: bulky mediastinum			
Yes v no	9.9	1.3-74.1	.025
Model 2: residual mediastinal abnormality			
Yes v no	7.6	1.7-33.3	.007

(1) considering all patients with contiguous intrathoracic extension as stage IIE independently of the number of sites involved, the distribution of patients among the four risk groups of the age-adjusted IPI was: 40 low risk, 32 low-intermediate, 19 high-intermediate, and five high risk; (2) considering patients with more than one contiguous extranodal site as stage IV, the breakdown by risk groups was 30 low risk, 30 low-intermediate, 24 high-intermediate, and 12 high risk. In both analyses, no statistically significant differences in response, overall survival, and relapse-free survival were observed among the first three IPI groups. Only patients categorized as high risk (five patients using the first modality of stage classification; 12 using the second modality) showed a significantly worse overall survival (P = .009 and P = .011, respectively). Table 5 shows the proportion of response, overall survival, and relapse-free survival of the four risk groups of the age-adjusted IPI assessed according to the two different definitions of stage.

DISCUSSION

This study shows in a large population of patients that primary MBL is a distinct clinicopathologic entity that differs from other NHL in presentation and modality of spread. Typical features include presentation in almost all cases with symptoms of a rapidly enlarging mediastinal mass of upper anterior mediastinum with high frequency (47%) of SVCS, bulky mediastinal tumor (73%), and intrathoracic circumferential extension to adjacent structures (57%).

Many reports describe the homogeneous aspects of this tumor, also underlying its aggressive course.[9,13-15] In this study, 65% of patients responded to first-line therapy with doxorubicin containing regimens and 35% were primary refractory. Twenty-eight percent of responders relapsed. The 3-year overall survival rate was 52%, and 82% for responders (Fig 2). The disease-free survival rate of the 64 responders was 71% at 3 years. Most relapses (15

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Table 5. Outcome of 96 Patients with MBL ≤ 60 Years According to Risk Group Defined by the Age-Adjusted International Prognostic Index

Score	No. of Patients	% Response	3-Year Survival		3-Year Relapse-Free Survival	
			%	SE	%	SE
IPI 1						
0	40	72	58	8.06	80	8.15
1	32	66	55	8.99	65	10.85
2	19	58	48	11.67	72	14.63
3	5	20	—*		—	
IPI 2						
0	30	70	55	9.30	76	10.02
1	30	67	58	9.53	70	11.64
2	24	71	62	10.02	76	10.80
3	12	33	17	8.53	25	6.75

NOTE. Patients with > 1 contiguous extranodal site of extension in the thorax were considered alternatively stage IIE in IPI 1, stage IV in IPI 2.
*All patients died within 14 months from diagnosis.

of 18; 83%) occurred within 18 months of diagnosis, indicating that patients free of disease after this period are likely to be cured. The outcome of both primary refractory and relapsing patients (53% of this series) was poor. Of 35 patients refractory to first-line CHT, none responded to salvage treatment, and of 18 patients who relapsed, only four (22%) responded.

These results, like those of other studies,[8,13,15,27] clearly demonstrate that a good proportion of patients responds well to intensive CHT, achieving long-term disease-free survival and cure. However, a substantial number of patients are from the onset highly refractory to anthracycline-containing regimens, or relapse during the first months after the end of treatment. The early identification of MBL patients at high risk of NR or relapse would help to assign these cases to more intensive treatments.

While prognostic factors for aggressive lymphomas are well defined, specific prognostic studies on MBL are scarce. Therefore, it is uncertain whether the established prognostic indexes for aggressive lymphomas may be applied to MBL. We evaluated the prognostic value of the age-adjusted IPI in 96 patients of this series, age ≤ 60 years. As the predictivity of the model could be biased by classification of tumor stage as localized (stage IIE) or advanced (stage IV) based only on the number of contiguous extranodal sites in the thorax, the IPI score was calculated using two alternative modalities of stage assignment (Table 5). In both analyses, no significant differences in response and survival were found among the first three IPI groups. Only the relatively small number of patients categorized as high risk (five using the first modality of stage classification; 12 using the second modality) showed a significantly worse outcome. Although the IPI system shows prognostic value in aggressive NHL, it seems of limited prognostic power in MBL, probably because of inherent differences in biology, presentation and modality of spread. We could not evaluate the impact of prognostic models based on initial serum levels of β2-M and LDH.[30] It is worthwhile to note that all MBL patients of this seris tested for β2-M had normal levels despite bulky tumor and aggressive behavior. This serologic pattern, as previously reported,[31] further differentiates this tumor among NHLs and suggests caution in the use of β2-M levels in prognostic analysis of MBL.

Few studies have specifically addressed prognostic factors for MBL. Jacobson et al,[8] in 30 patients mostly treated with CHOP plus RT, reported a 59% 5-year failure-free survival rate, with bulky disease and a compromised drug dose-intensity as the only prognostic factors. In 57 patients treated with doxorubicin-containing regimens, Kirn et al[13] reported a 50% chance of surviving disease-free, and indicated pleural effusion, bulky mediastinum, multiple extranodal extension, and incomplete response as predictors of poor outcome. In 141 patients treated with intensive CHT with no RT, Cazals-Hatem et al[27] reported a 66% 3-year survival rate and found that poor performance status and persistence of a residual mass after treatment influenced survival.

The aim of the present study was to investigate the treatment outcome and prognostic factors in a large series of patients with MBL treated with doxorubicin-containing regimens. Among risk factors associated in univariate analysis with NR to CHT (poor performance status, pericardial effusion, high serum LDH levels, and low RDI of doxorubicin and cyclophosphamide), multivariate analysis selected poor performance status and pericardial effusion as the two most important independent factors of initial failure (Table 2). In addition, failure to achieve at least a PR after the first 6 to 9 weeks of first-line therapy invariably predicted resistance to subsequent salvage treatments. Identification at diagnosis, or early in treatment, of high-risk patients unlikely to respond to

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conventional CHT seems an important step in the management of this aggressive lymphoma. Such patients might be candidates for intensified approaches. Because failure to achieve an initial response to front-line CHT is associated with a very short survival, it is not surprising that the same features that correlated with an increased risk of NR were also associated with an increased risk of death in survival analysis (Table 3). For responding patients, bulky mediastinum was the only presenting feature significantly associated with poor relapse-free survival at multivariate analysis (Table 4). Bulky presentation was also strictly associated with the persistence of mediastinal abnormality at the end of CHT. All relapses occurred among patients with residual mediastinal mass, 88% of whom were bulky at presentation.

This analysis underlines the negative prognostic relevance of bulky tumor, poor performance status, a compromised drug dose-intensity, and incomplete response to therapy in MBL, as emerged from studies by Jacobson et al,[8] Kirn et al,[13] and Cazals-Hatem et al.[27] However, in contrast to Kirn's study, we did not find pleural effusion as a predictor of poor outcome. Interestingly, the histomorphologic variability, which within this lymphoma entity is considerable, had no predictive value.

In agreement with prior observations,[13-15,19,26,27] this study shows that the majority of patients with MBL who present with bulky disease have residual radiographic mediastinal abnormalities of uncertain significance at the completion of CHT. Residual mediastinal mass after CHT does not necessarily represent active disease.[32] In fact, of patients with apparently incomplete response, the majority remained free of disease and will probably be cured. However, others relapsed a few months after response. This suggests that such patients, despite apparently good clinical response, had a significant burden of active disease at the end of CHT and were in fact occult induction failures. In the absence of studies on ^{67}Ga avidity in the residual mass, posttreatment discrimination between residual active tumor and fibrosis on the basis of CT scan only is impossible. In the study by Kirn et al,[13] any radiographic residual tumor mass was associated with increased risk of relapse, but no cutoff size of the residual mass could be identified below which relapse was less likely. Residual ^{67}Ga avidity after CHT was associated with increased risk of relapse. This technique, capable of discriminating residual fibrotic tissue from active tumor, may further contribute to the early identification of induction failures.[33]

Consolidative mediastinal RT is common for patients with bulky mediastinal disease. Because most patients in this study, as in other studies, had consolidation RT, its role in the eradication of residual disease is hard to assess. RT may possibly benefit some patients with residual active disease. However, in this study, it was ineffective as salvage treatment on CHT-resistant disease. Also in the study by Kirn et al,[13] patients who remained ^{67}Ga-positive after CHT seemed incurable by RT. A recent study obtained a favorable survival rate using aggressive induction and consolidation CHT without RT.[27]

In conclusion, MBL is an aggressive NHL with peculiar clinicopathologic features. One third of patients were refractory to first-line therapy with doxorubicin-containing regimens. Furthermore, among responders, a substantial proportion relapsed early. Both primarily resistant and relapsing patients are usually insensitive to chemotherapeutic salvage regimens. This study on the prognostic assessment of patients with MBL followed two steps: (1) early identification of cases at high risk of NR to conventional CHT; (2) among responders, identification of those at higher risk of relapse. Among features at presentation, poor performance status and pericardial effusion were the two most important independent risk factors related to NR and poor survival. Inadequate response after the first courses of front-line CHT was an additional clinical feature that predicted failure of subsequent treatments. These early predictors of NR should help to select high-risk patients for more intensive therapy from the beginning or after the first weeks of treatment. Prognostic assessment of responders indicated that patients who achieve a radiographic CR after CHT will remain disease-free, while those showing residual mediastinal abnormality are at risk of relapse. This last feature is closely related with bulky mediastinum at presentation. This strongly emphasizes the need for using more sensitive restaging techniques to differentiate true remission with residual scar tissue from responses with viable residual tumor. The latter might then be submitted to more aggressive forms of therapy. Early high-dose treatments or high-dose consolidation of response could modify the poor prognosis of these patients.

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Set     Items   Description
S1     117992   REFRACTORY
S2       8434   CD20
S3        434   S1 AND S2
S4    1309423   RADIOLABEL? OR RADIO?
S5        106   S3 AND S4
S6     214151   LYMPHOMA
S7        104   S5 AND S6
S8         13   S7 AND PY<=1998
S9          9   RD (unique items)
S10        35   AU=DAVIS T AND PY=1999
S11      3802   LYMPHOMA AND CD20
S12         0   S10 AND S11
S13      8434   CD20
S14         0   S10 AND S13
S15    214151   LYMPHOMA
S16         0   S10 AND S15
S17        24   RD S10 (unique items)
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>>>  or undefined in one or more files.
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         1070537  RESEARCH
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? s au= Davis T
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? s lymphoma or cd20
          214151  LYMPHOMA
            8434  CD20
     S20  218783  LYMPHOMA OR CD20
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          218783  S20
     S21      20  S19 AND S20
? rd
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>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S22      14  RD (unique items)
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 22/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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11007802   20549991   PMID: 11098509
   Clinical  trials referral resource. Current clinical trials of the anti-
CD20 monoclonal antibody rituximab.
  Davis T; Gore-Langton R E; Cheson B D
  Oncology  (Williston  Park,  N.Y.) (UNITED  STATES)   Oct 2000,  14  (10)
 p1437, 1440-3,  ISSN 0890-9091   Journal Code: 8712059
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed

   Clinical  trials referral resource. Current clinical trials of the anti-
CD20 monoclonal antibody rituximab.
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Davis T; Gore-Langton R E; Cheson B D
Descriptors: Antibodies, Monoclonal--therapeutic use--TU; *Antineoplastic Agents--therapeutic use--TU; ***Lymphoma**, B-Cell--therapy--TH; ***Lymphoma**, Non-Hodgkin--therapy--TH

22/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10031591 99035039 PMID: 9816191
Yttrium-90-labeled anti-**CD20** monoclonal antibody therapy of recurrent B-cell **lymphoma**.
Knox S J; Goris M L; Trisler K; Negrin R; **Davis T**; Liles T M; Grillo-Lopez A; Chinn P; Varns C; Ning S C; Fowler S; Deb N; Becker M; Marquez C; Levy R
Departments of Radiation Oncology, Diagnostic Radiology, Division of Nuclear Medicine, Stanford University School of Medicine, Stanford, California, 94305, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Mar 1996, 2 (3) p457-70, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA-34233; CA; NCI; MO1-RR00070; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A Phase I/II dose escalation study of 90Y-murine anti-**CD20** monoclonal antibody (mAb) in patients with recurrent B-cell **lymphoma** was performed. The primary objectives of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-**CD20** mAb on the biodistribution of 111In-anti-**CD20** mAb; (b) to determine the maximal tolerated dose of 90Y-anti-**CD20** mAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of 90Y-anti-**CD20** mAb in patients with recurrent B-cell **lymphoma**. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's **lymphoma** were treated. Biodistribution studies with 111In-anti-**CD20** mAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of approximately 13.5, 20, 30, 40, and 50 mCi 90Y-anti-**CD20** mAb. Three patients were retreated at the 40-mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of 90Y-anti-**CD20** mAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ months following treatment. Radioimmunotherapy with </=50 mCi 90Y-anti-**CD20** mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell **lymphoma**. Doses of </=40 mCi 90Y-anti-**CD20** mAb were not myeloablative.

Yttrium-90-labeled anti-**CD20** monoclonal antibody therapy of recurrent B-cell **lymphoma**.
Knox S J; Goris M L; Trisler K; Negrin R; **Davis T**; Liles T M; Grillo-Lopez A; Chinn P; Varns C; Ning S C; Fowler...
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CD20 mAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of approximately 13.5, 20, 30, 40, and 50 mCi 90Y-anti-**CD20** mAb. Three patients were retreated at the 40-mCi dose level. The use of unlabeled...

... significant toxicity was myelosuppression. The overall response rate following a single dose of 90Y-anti-**CD20** mAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ months following treatment. Radioimmunotherapy with </=50 mCi 90Y-anti-**CD20** mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell **lymphoma**. Doses of </=40 mCi 90Y-anti-**CD20** mAb were not myeloablative.

Descriptors: Antibodies, Monoclonal--therapeutic use--TU; *Antigens, **CD20**--immunology--IM; ***Lymphoma**, B-Cell--radiotherapy--RT; *Radioimmunotherapy; *Yttrium Radioisotopes--therapeutic use--TU

Chemical Name: Antibodies, Monoclonal; Antigens, **CD20**; Yttrium Radioisotopes

22/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09570478 97454394 PMID: 9310469

IDEC-C2B8 (Rituximab) anti-**CD20** monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's **lymphoma**.

Maloney D G; Grillo-Lopez A J; White C A; Bodkin D; Schilder R J; Neidhart J A; Janakiraman N; Foon K A; Liles T M; Dallaire B K; Wey K; Royston I; **Davis T**; Levy R

Department of Medicine, Stanford University, CA, USA.

Blood (UNITED STATES) Sep 15 1997, 90 (6) p2188-95, ISSN 0006-4971 Journal Code: 7603509

Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article; Multicenter Study

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

IDEC-C2B8 is a chimeric monoclonal antibody (MoAb) directed against the B-cell-specific antigen **CD20** expressed on non-Hodgkin's lymphomas (NHL). The MoAb mediates complement and antibody-dependent cell-mediated cytotoxicity and has direct antiproliferative effects against malignant B-cell lines in vitro. Phase I trials of single doses up to 500 mg/m2 and 4 weekly doses of 375 mg/m2 showed clinical responses with no dose-limiting toxicity. We conducted a phase II, multicenter study evaluating four weekly infusions of 375 mg/m2 IDEC-C2B8 in patients with relapsed low-grade or follicular NHL (Working Formulation groups A-D). Patients were monitored for adverse events, antibody pharmacokinetics, and clinical response. Thirty-seven patients with a median age of 58 years (range, 29 to 81 years) were treated. All patients had relapsed after chemotherapy (median of 2 prior regimens) and 54% had failed aggressive chemotherapy. Infusional side effects (grade 1-2) consisting of mild fever, chills, respiratory symptoms, and occasionally hypotension were observed mostly with the initial antibody infusion and were rare with subsequent doses. Peripheral blood B-cell depletion occurred rapidly, with recovery beginning 6 months posttreatment. There were no significant changes in mean IgG levels and infections were not increased over what would be expected in this population. Clinical remissions were observed in 17 patients (3 complete remissions and 14 partial remissions), yielding an intent to treat response rate of 46%. The onset of these tumor responses was as soon as 1 month posttreatment and reached a maximum by 4 months posttreatment. In the 17 responders, the median time to progression was 10.2 months (5 patients exceeding 20 months). Likelihood of tumor response was associated with a follicular histology, with the ability to sustain a high serum level of antibody after

the first infusion, and with a longer duration of remission to prior chemotherapy. One patient developed a detectable but not quantifiable immune response to the antibody that had no clinical significance. IDEC-C2B8 in a dose of 375 mg/m2 weekly for 4 weeks has antitumor activity in patients with relapsed low-grade or follicular NHL. Results with this brief, outpatient treatment compare favorably with results with standard chemotherapy, and IDEC-C2B8 has a better safety profile. Further studies evaluating IDEC-C2B8 in other types of **lymphoma** either alone or combined with chemotherapy are warranted.

IDEC-C2B8 (Rituximab) anti-**CD20** monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's **lymphoma**.
...Janakiraman N; Foon K A; Liles T M; Dallaire B K; Wey K; Royston I; **Davis T**; Levy R
IDEC-C2B8 is a chimeric monoclonal antibody (MoAb) directed against the B-cell-specific antigen **CD20** expressed on non-Hodgkin's lymphomas (NHL). The MoAb mediates complement and antibody-dependent cell...

... C2B8 has a better safety profile. Further studies evaluating IDEC-C2B8 in other types of **lymphoma** either alone or combined with chemotherapy are warranted.
Descriptors: Antibodies, Monoclonal--therapeutic use--TU; *Antigens, **CD20**--immunology--IM; ***Lymphoma**, Non-Hodgkin--therapy--TH
Chemical Name: Antibodies, Anti-Idiotypic; Antibodies, Monoclonal; Antigens, **CD20**; Chimeric Proteins; rituximab

22/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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07787964 93313964 PMID: 8391931
CD30 antigen, a marker for Hodgkin's **lymphoma**, is a receptor whose ligand defines an emerging family of cytokines with homology to TNF.
Smith C A; Gruss H J; **Davis T**; Anderson D; Farrah T; Baker E; Sutherland G R; Brannan C I; Copeland N G; Jenkins N A; et al
Immunex Research and Development Corporation, Seattle, Washington 98101.
Cell (UNITED STATES) Jul 2 1993, 73 (7) p1349-60, ISSN 0092-8674 Journal Code: 0413066
Contract/Grant No.: N01-CO-74101; CO; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
CD30 is a surface marker for neoplastic cells of Hodgkin's **lymphoma** and shows sequence homology to members of the tumor necrosis factor (TNF) receptor superfamily. Using a chimeric probe consisting of the extracellular domain of CD30 fused to truncated immunoglobulin heavy chains, we expression cloned the cDNA cognate from the murine T cell clone 7B9. The encoded protein is a 239 amino acid type II membrane protein whose C-terminal domain shows significant homology to TNF alpha, TNF beta, and the CD40L. Cross-hybridization to an induced peripheral blood T cell cDNA library yielded the human homolog, which is 72% identical at the amino acid level. The recombinant human ligand enhances the proliferation of CD3-activated T cells yet induces differential responses, including cell death, in several CD30+ **lymphoma**-derived clones. The human and murine genes map to 9q33 and the proximal region of chromosome 4, respectively.

CD30 antigen, a marker for Hodgkin's **lymphoma**, is a receptor whose ligand defines an emerging family of cytokines with homology to TNF.
Smith C A; Gruss H J; **Davis T**; Anderson D; Farrah T; Baker E; Sutherland G R; Brannan C I; Copeland N...
CD30 is a surface marker for neoplastic cells of Hodgkin's **lymphoma** and shows sequence homology to members of the tumor necrosis factor (TNF)

receptor superfamily. Using...

... of CD3-activated T cells yet induces differential responses, including cell death, in several CD30+ **lymphoma**-derived clones. The human and murine genes map to 9q33 and the proximal region of...

22/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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07613147 93128208 PMID: 8420254
Endometriosis of the small intestine presenting as a protein-losing enteropathy.
Henley J D; Kratzer S S; Seo I S; **Davis T**
Department of Pathology, Wishard Memorial Hospital-Indiana University School of Medicine, Indianapolis.
American journal of gastroenterology (UNITED STATES) Jan 1993, 88 (1) p130-3, ISSN 0002-9270 Journal Code: 0421030
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A 46-yr-old multiparous cachetic woman presented with severe hypoalbuminemia in the absence of liver disease, proteinuria, and/or protracted starvation. The clinical presentation and work-up was indicative of protein-losing enteropathy. She developed an acute partial small bowel obstruction, and a presumptive diagnosis of **lymphoma** of the small intestine was entertained. Surgical resection of the terminal ileum revealed transmural involvement of the bowel by endometriosis. Her postoperative recovery was uneventful, with return of her serum albumin levels to normal.
Henley J D; Kratzer S S; Seo I S; **Davis T**
... losing enteropathy. She developed an acute partial small bowel obstruction, and a presumptive diagnosis of **lymphoma** of the small intestine was entertained. Surgical resection of the terminal ileum revealed transmural involvement...

22/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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01375806 72126323 PMID: 4622005
Response of peripheral blood lymphocytes from normal, hypogammaglobulinemic and chronic lymphocytic leukemic patients.
Rodey G E; **Davis T**; Quie P G
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jan 1972, 108 (1) p178-82, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Rodey G E; **Davis T**; Quie P G
...; Cell Adhesion; Cells, Cultured; Chromatography, DEAE-Cellulose; Chronic Disease; Immunity, Cellular; Immunodiffusion; Lectins--pharmacology --PD; **Lymphoma**--immunology--IM; Myasthenia Gravis--immunology--IM; Thymidine--metabolism--ME; Thymus Gland--immunology--IM; Tritium

22/3,K,AB/7 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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11856764 BIOSIS NO.: 199900102873
Rituximab: Phase II (PII) retreatment (ReRx) study in patients (PTS) with low-grade or follicular (LG/F) NHL.
AUTHOR: **Davis T**(a); Levy R; White C A; Czuczman M; McLaughlin P; Link B; Varns C; Weaver R; Grillo-Lopez A J
AUTHOR ADDRESS: (a)NCCI, Rockville, MD**USA
JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p414A Nov. 15, 1998
CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1998

AUTHOR: **Davis T**...
DESCRIPTORS:
DISEASES: NHL {non-Hodgkin's **lymphoma**}--
CHEMICALS & BIOCHEMICALS: Rituximab {Rituxan, anti-**CD20** monoclonal antibody...

22/3,K,AB/8 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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11415502 BIOSIS NO.: 199800196834
Therapy of B cell **lymphoma** with anti-**CD20** antibodies can result in relapse with loss of **CD20** expression.
AUTHOR: **Davis T**; Levy R
AUTHOR ADDRESS: Stanford Univ., Stanford, CA 94305**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p435 March, 1998
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

Therapy of B cell **lymphoma** with anti-**CD20** antibodies can result in relapse with loss of **CD20** expression.
AUTHOR: **Davis T**...
DESCRIPTORS:
DISEASES: B-cell **lymphoma**--
CHEMICALS & BIOCHEMICALS: anti-**CD20** antibody...

...**CD20** protein

22/3,K,AB/9 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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11287246 BIOSIS NO.: 199800068578
Retreatments with RITUXAN (Rituximab, Idec-C2B8) have significant efficacy, do not cause hama, and are a viable minimally toxic alternative in relapsed or refractory non-Hodgkin's **lymphoma** (NHL).
AUTHOR: **Davis T**(a); Levy R; White C A; Maloney D G; Link B; Velasquez W S; Varns C; Gardner C; Grillo-Lopez A J
AUTHOR ADDRESS: (a)Stanford Univ., Stanford, CA**USA
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p509A Nov. 15, 1997

CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997

...hama, and are a viable minimally toxic alternative in relapsed or refractory non-Hodgkin's **lymphoma** (NHL).
AUTHOR: **Davis T**...
DESCRIPTORS:
DISEASES: follicular non-Hodgkin's **lymphoma**-...

...non-Hodgkin's **lymphoma**--

22/3,K,AB/10 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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10165118 BIOSIS NO.: 199698620036
IDEC-C2B8 anti-**CD20** antibody: Results of long-term follow-up of relapsed NHL phase II trial patients.
AUTHOR: Maloney D G; Grillo-Lopez A J; Bodkin D; White C; Foon K; Schilder R J; Neidhart J; Janakiraman N; Waldichuik C; **Davis T**; Dallaire B K ; Royston L; Levy R
AUTHOR ADDRESS: Stanford Univ. Med. Cent., Palo Alto, CA**USA
JOURNAL: Blood 86 (10 SUPPL. 1):p54A 1995
CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1995

IDEC-C2B8 anti-**CD20** antibody: Results of long-term follow-up of relapsed NHL phase II trial patients.
...AUTHOR: **Davis T**
MISCELLANEOUS TERMS: ...B-CELL **LYMPHOMA**;

22/3,K,AB/11 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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11104479 Genuine Article#: 608AE Number of References: 47
Title: Phase 1 trial of the novel bispecific molecule H22xKi-4 in patients with refractory Hodgkin **lymphoma** (ABSTRACT AVAILABLE)
Author(s): Borchmann P; Schnell R; Fuss I; Manzke O; **Davis T**; Lewis LD; Behnke D; Wickenhauser C; Schiller P; Diehl V; Engert A (REPRINT)
Corporate Source: Univ Cologne,Innere Med Klin 1,Joseph Stelzmannstr 9/D-50924 Cologne//Germany/ (REPRINT); Univ Cologne,Innere Med Klin 1,D-50924 Cologne//Germany/; Univ Cologne,Inst Pathol,D-5000 Cologne//Germany/; Medarex,Annandale//NJ/; Dartmouth Hitchcock Med Ctr,Lebanon//NH/03766; Dartmouth Coll Sch Med,Lebanon//NH/
Journal: BLOOD, 2002, V100, N9 (NOV 1), P3101-3107
ISSN: 0006-4971 Publication date: 20021101
Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA
Language: English Document Type: ARTICLE
Abstract: CD30 is an excellent target for immunotherapy of Hodgkin **lymphoma** (HL) because it is overexpressed on Hodgkin and Reed-Sternberg cells. We developed a novel bispecific molecule (BSM)

consisting of F(ab') fragments derived from the murine anti-CD30 monoclonal antibody (MoAb) Ki-4 and the humanized CD64-specific MoAb H22. In vitro experiments of H22xKi-4 demonstrated specific phagocytosis of HL-derived cell lines. Patients (pts) with refractory CD30(+) HL were treated with escalating doses of H22xKi-4 at doses of 1, 2.5, 5, 10, and 20 mg/m(2)/d, respectively. (administered intravenously on days 1, 3, 5, and 7). The main study objectives were to determine the maximum tolerated dose and the dose-limiting toxicities of H22xKi-4, to define its pharmacokinetic profile, and to document clinical response. Ten pts Were enrolled and are evaluable for toxicity and response. Side effects were transient and mild with hypotension (4 of 10), tachycardia (6 of 1 0), fatigue (110 of 10), and fever (2 of 10 grade 1, 3 of 10 grade II) Pharmacokinetic (PK) data revealed an elimination half-life of 11.1 hours, resulting in a significant accumulation of H22xKi-4. The BSM was shown to bind to both monocytet and malignant cells. Response to H22xKi-4 included 1 complete remission (CR), 3 partial remissions (PR), and 4 pts with stable disease. The new BSM H22xKi-4 can be given safely to, pts with refractory CD30+ HL in doses up to 80 mg/m(2) per cycle. Although this dose is not the maximum tolerated dose (MTD) as defined by toxicity criteria, surrogate parameters suggest a biologic effective regimen. H22xKi-4 shows activity in heavily pretreated HL patients warranting further clinical evaluation. (C) 2002 by The American Society of Hematology.

Title: Phase 1 trial of the novel bispecific molecule H22xKi-4 in patients with refractory Hodgkin **lymphoma**

Author(s): Borchmann P; Schnell R; Fuss I; Manzke O; **Davis T**; Lewis LD; Behnke D; Wickenhauser C; Schiller P; Diehl V; Engert A (REPRINT)

Abstract: CD30 is an excellent target for immunotherapy of Hodgkin **lymphoma** (HL) because it is overexpressed on Hodgkin and Reed-Sternberg cells. We developed a novel...

22/3,K,AB/12 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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10242279 Genuine Article#: 491WY Number of References: 0

Title: The bispecific molecule H22xKi-4: Proof of principle study in patients with refractory Hodgkins **lymphoma**.

Author(s): Borchmann P; Fuss I; Schnell R; Manske O; **Davis T**; Engert A

Corporate Source: Univ Cologne,Innere Med Klin,Cologne//Germany/; Medarex Inc,Annandale//NJ/

Journal: BLOOD, 2001, V98, N11,1 (NOV 16), P466A-466A

ISSN: 0006-4971 Publication date: 20011116

Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA

Language: English Document Type: MEETING ABSTRACT

Title: The bispecific molecule H22xKi-4: Proof of principle study in patients with refractory Hodgkins **lymphoma**.

Author(s): Borchmann P; Fuss I; Schnell R; Manske O; **Davis T**; Engert A

22/3,K,AB/13 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06699187 Genuine Article#: ZL271 Number of References: 1

Title: Peripheral T-cell **lymphoma** after anti-**CD20** antibody therapy - In reply (vol 16, pg 1636, 1998)

Author(s): Maloney DG (REPRINT) ; **Davis T**; Levy R

Corporate Source: UNIV WASHINGTON,FRED HUTCHINSON CANC RES CTR/SEATTLE//WA/98195 (REPRINT)
Journal: JOURNAL OF CLINICAL ONCOLOGY, 1998, V16, N5 (MAY), P2001-2001
ISSN: 0732-183X Publication date: 19980500
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399
Language: English Document Type: CORRECTION, ADDITION

Title: Peripheral T-cell **lymphoma** after anti-**CD20** antibody therapy - In reply (vol 16, pg 1636, 1998)
Author(s): Maloney DG (REPRINT) ; **Davis T**; Levy R

22/3,K,AB/14 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06298655 Genuine Article#: YG424 Number of References: 0
Title: Retreatments with RITUXAN(TM) (Rituximab, Idec-C2B8) have significant efficacy, do not cause hama, and are a viable minimally toxic alternative in relapsed or refractory non-Hodgkin's **lymphoma** (NHL).
Author(s): **Davis T**; Levy R; White CA; Maloney DG; Link B; Velasquez WS; Varns C; Gardner C; GrilloLopez AJ
Corporate Source: ST LOUIS UNIV,MED CTR/ST LOUIS//MO/; STANFORD UNIV,/STANFORD//CA/94305; IDEC PHARMACEUT CORP,/SAN DIEGO//CA/; FRED HUTCHINSON CANC RES CTR,/SEATTLE//WA/98104; UNIV IOWA,/IOWA CITY//IA/
Journal: BLOOD, 1997, V90, N10,1,1 (NOV 15), P2269-2269
ISSN: 0006-4971 Publication date: 19971115
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399
Language: English Document Type: MEETING ABSTRACT

...Title: hama, and are a viable minimally toxic alternative in relapsed or refractory non-Hodgkin's **lymphoma** (NHL).
Author(s): **Davis T**; Levy R; White CA; Maloney DG; Link B; Velasquez WS; Varns C; Gardner C...
?

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? s refractory
      S1  117992  REFRACTORY
? s cd20
      S2    8434  CD20
? s s1 and s2
          117992  S1
            8434  S2
      S3     434  S1 AND S2
? s radiolabel? or radio?
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>>>File 55 processing for RADIO? stopped at RADIOTHERMAL
>>>File 34 processing for RADIO? stopped at RADIOOPAQUE
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         1284588  RADIO?
      S4 1309423  RADIOLABEL? OR RADIO?
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         1309423  S4
      S5     106  S3 AND S4
? s lymphoma
      S6  214151  LYMPHOMA
? s s5 and s6
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          214151  S6
      S7     104  S5 AND S6
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Processing
Processing
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? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
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3/6

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 9/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

08928841   96283115   PMID: 8683227
  Iodine-131-anti-B1 radioimmunotherapy for B-cell lymphoma.
  Kaminski M S; Zasadny K R; Francis I R; Fenner M C; Ross C W; Milik A W;
Estes J; Tuck M; Regan D; Fisher S; Glenn S D; Wahl R L
  Department of Internal Medicine, University of Michigan, Ann Arbor
48109-0724, USA. mkaminsk@umich.edu
  Journal of clinical oncology : official journal of the American Society
of Clinical Oncology (UNITED STATES)  Jul 1996,  14 (7) p1974-81,
ISSN 0732-183X  Journal Code: 8309333
  Contract/Grant No.: M01-RR-00042; RR; NCRR; PO1-CA-42768; CA; NCI;
R01-CA56794; CA; NCI
  Document type: Clinical Trial; Clinical Trial, Phase I; Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  PURPOSE: The CD20 B-lymphocyte surface antigen expressed by B-cell
lymphomas is an attractive target for radioimmunotherapy, treatment using
radiolabeled antibodies. We conducted a phase I dose-escalation trial
to assess the toxicity, tumor targeting, and efficacy of nonmyeloablative
doses of an anti-CD20 monoclonal antibody (anti-B1) labeled with
```

iodine-131 (131I) in 34 patients with B-cell **lymphoma** who had failed chemotherapy. PATIENTS AND METHODS: Patients were first given tracelabeled doses of 131I-labeled anti-B1 (15 to 20 mg, 5 mCi) to assess **radiolabeled** antibody biodistribution, and then a radioimmunotherapeutic dose (15 to 20 mg) labeled with a quantity of 131I that would deliver a specified centigray dose of whole-body radiation predicted by the tracer dose. Whole-body radiation doses were escalated from 25 to 85 cGy in sequential groups of patients in 10-cGy increments. To evaluate if **radiolabeled** antibody biodistribution could be optimized, initial patients were given one or two additional tracer doses on successive weeks, each dose preceded by an infusion of 135 mg of unlabeled anti-B1 one week and 685 mg the next. The unlabeled antibody dose resulting in the most optimal tracer biodistribution was also given before the radioimmunotherapeutic dose. Later patients were given a single tracer dose and radioimmunotherapeutic dose preceded by infusion of 685 mg of unlabeled anti-B1. RESULTS: Treatment was well tolerated. Hematologic toxicity was dose-limiting, and 75 cGy was established as the maximally tolerated whole-body radiation dose. Twenty-eight patients received radioimmunotherapeutic doses of 34 to 161 mCi, resulting in complete remission in 14 patients and a partial response in eight. All 13 patients with low-grade **lymphoma** responded, and 10 achieved a complete remission. Six of eight patients with transformed **lymphoma** responded. Thirteen of 19 patients whose disease was resistant to their last course of chemotherapy and all patients with chemotherapy-sensitive disease responded. The median duration of complete remission exceeds 16.5 months. Six patients remain in complete remission 16 to 31 months after treatment. CONCLUSION: Nonmyeloablative radioimmunotherapy with 131I-anti-B1 is associated with a high rate of durable remissions in patients with B-cell **lymphoma refractory** to chemotherapy.

Iodine-131-anti-B1 radioimmunotherapy for B-cell **lymphoma**.
Jul **1996**,
PURPOSE: The **CD20** B-lymphocyte surface antigen expressed by B-cell lymphomas is an attractive target for radioimmunotherapy, treatment using **radiolabeled** antibodies. We conducted a phase I dose-escalation trial to assess the toxicity, tumor targeting, and efficacy of nonmyeloablative doses of an anti-**CD20** monoclonal antibody (anti-B1) labeled with iodine-131 (131I) in 34 patients with B-cell **lymphoma** who had failed chemotherapy. PATIENTS AND METHODS: Patients were first given tracelabeled doses of 131I-labeled anti-B1 (15 to 20 mg, 5 mCi) to assess **radiolabeled** antibody biodistribution, and then a radioimmunotherapeutic dose (15 to 20 mg) labeled with a quantity...

... to 85 cGy in sequential groups of patients in 10-cGy increments. To evaluate if **radiolabeled** antibody biodistribution could be optimized, initial patients were given one or two additional tracer doses...

... in 14 patients and a partial response in eight. All 13 patients with low-grade **lymphoma** responded, and 10 achieved a complete remission. Six of eight patients with transformed **lymphoma** responded. Thirteen of 19 patients whose disease was resistant to their last course of chemotherapy...

...B1 is associated with a high rate of durable remissions in patients with B-cell **lymphoma refractory** to chemotherapy.
Descriptors: **Lymphoma**, B-Cell--radiotherapy--RT; *Radioimmunotherapy; Adult; Aged; Antibodies, Monoclonal; Antigens, **CD20**--immunology--IM; Dose-Response Relationship, Radiation; Iodine Radioisotopes--therapeutic use--TU; **Lymphoma**, B-Cell--immunology--IM; Middle Age; Radioimmunotherapy--adverse effects--AE; Remission Induction
Chemical Name: Antibodies, Monoclonal; Antigens, **CD20**; Iodine Radioisotopes; iodine-131 anti-B1 antibody

9/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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06239608 89328477 PMID: 2666588

Treatment of **refractory** non-Hodgkin's **lymphoma** with **radiolabeled** MB-1 (anti-CD37) antibody.

Press O W; Eary J F; Badger C C; Martin P J; Appelbaum F R; Levy R; Miller R; Brown S; Nelp W B; Krohn K A; et al

Department of Medicine (Division of Oncology), Fred Hutchinson Cancer Research Center, University of Washington, Seattle.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Aug **1989**, 7 (8) p1027-38, ISSN 0732-183X Journal Code: 8309333

Contract/Grant No.: CA15704; CA; NCI; CA18029; CA; NCI; CA44991; CA; NCI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The biodistribution, toxicity, and therapeutic potential of anti-CD37 monoclonal antibody (MoAb) MB-1 labeled with iodine 131 (131I) was evaluated in ten patients with advanced-, low- or intermediate-grade non-Hodgkin's lymphomas who failed conventional treatment. Sequential dosimetric studies were performed with escalating amounts of antibody MB-1 (0.5, 2.5, 10 mg/kg) trace-labeled with 5 to 10 mCi 131I. Serial tumor biopsies and gamma camera imaging showed that the 10 mg/kg MoAb dose yielded the best MoAb biodistribution in the ten patients studied. Biodistribution studies in the five patients with splenomegaly and tumor burdens greater than 1 kg indicated that not all tumor sites would receive more radiation than normal organs, and these patients were therefore not treated with high-dose radioimmunotherapy. The other five patients did not have splenomegaly and had tumor burdens less than 0.5 kg; all five patients in this group showed preferential localization and retention of MoAb at tumor sites. Four of these patients have been treated with 131I (232 to 608 mCi) conjugated to anti-CD37 MoAb MB-1, delivering 850 to 4,260 Gy to tumor sites. Each of these four patients attained a complete tumor remission (lasting 4, 6, 11+, and 8+ months). A fifth patient, whose tumor did not express the CD37 antigen, was treated with 131I-labeled anti-**CD20** MoAb 1F5 and achieved a partial response. Myelosuppression occurred 3 to 5 weeks after treatment in all cases, but there were no other significant acute toxicities. Normal B cells were transiently depleted from the bloodstream, but immunoglobulin (Ig) levels were not affected, and no serious infections occurred. Two patients required reinfusion of previously stored autologous, purged bone marrow. Two patients developed asymptomatic hypothyroidism 1 year after therapy. The tolerable toxicity and encouraging efficacy warrant further dose escalation in this phase I trial.

Treatment of **refractory** non-Hodgkin's **lymphoma** with **radiolabeled** MB-1 (anti-CD37) antibody.

Aug **1989**,

... patient, whose tumor did not express the CD37 antigen, was treated with 131I-labeled anti-**CD20** MoAb 1F5 and achieved a partial response. Myelosuppression occurred 3 to 5 weeks after treatment...

Descriptors: Antibodies, Monoclonal--therapeutic use--TU; *Iodine Radioisotopes--therapeutic use--TU; ***Lymphoma**, Non-Hodgkin--therapy --TH...; effects--RE; Bone Marrow Transplantation; Iodine Radioisotopes --administration and dosage--AD; Iodine Radioisotopes--metabolism--ME; **Lymphoma**, Non-Hodgkin--metabolism--ME; **Lymphoma**, Non-Hodgkin --radiotherapy--RT; Middle Age; Radiotherapy Dosage; Remission Induction; Tissue Preservation

9/3,K,AB/3 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

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11556309 BIOSIS NO.: 199800337641
Dosimetry of I-131 Anti-B1 (anti-**CD20**) antibody for non-Hodgkin's **lymphoma**: Comparison of up-front treatment vs. chemotherapy-**refractory** patients.
AUTHOR: Rommelfanger S G; Zasadny K R; Gates V L; Fisher S J; Kaminski M S; Wahl R L
AUTHOR ADDRESS: Univ. Mich. Med. Cent., Ann Arbor, MI**USA
JOURNAL: Journal of Nuclear Medicine 39 (5 SUPPL.):p186P May, **1998**
CONFERENCE/MEETING: 45th Annual Meeting of the Society of Nuclear Medicine Toronto, Ontario, Canada June 7-11, 1998
SPONSOR: Society of Nuclear Medicine
ISSN: 0161-5505
RECORD TYPE: Citation
LANGUAGE: English
1998

Dosimetry of I-131 Anti-B1 (anti-**CD20**) antibody for non-Hodgkin's **lymphoma**: Comparison of up-front treatment vs. chemotherapy-**refractory** patients.
1998
DESCRIPTORS:
...MAJOR CONCEPTS: **Radiology** (Medical Sciences)
DISEASES: non-Hodgkin's **lymphoma**--
METHODS & EQUIPMENT: **radioimmunotherapy**--...

...**radiologic** method, therapeutic method

9/3,K,AB/4 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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11326381 BIOSIS NO.: 199800107713
Phase I/II trial of non-myeloablative iodine-131 anti-B-1 antibody (anti-**CD20**) therapy for relapsed and **refractory** B-cell non-Hodgkin's **lymphoma** (NHL).
AUTHOR: Shochat D(a); Langecker P J(a); Tidmarsh G F(a); Stagg R J(a); Wahl R L; Kaminski M S
AUTHOR ADDRESS: (a)Coulter Pharmaceutical Inc., Palo Alto, CA 94306**USA
JOURNAL: Tumor Biology 18 (SUPPL. 2):p31 Sept., **1997**
CONFERENCE/MEETING: Meeting on From Basic Cancer Research to Clinical Application held at the XXVth Anniversary Meeting of the International Society for Oncodevelopmental Biology and Medicine Montreux, Switzerland September 19-24, 1997
SPONSOR: International Society for Oncodevelopmental Biology and Medicine
ISSN: 1010-4283
RECORD TYPE: Citation
LANGUAGE: English
1997

Phase I/II trial of non-myeloablative iodine-131 anti-B-1 antibody (anti-**CD20**) therapy for relapsed and **refractory** B-cell non-Hodgkin's **lymphoma** (NHL).
1997
DESCRIPTORS:
DISEASES: B-cell non-Hodgkin's **lymphoma**--...

...blood and lymphatic disease, immune system disease, neoplastic disease, relapsed disease, treatment, **refractory** disease
METHODS & EQUIPMENT: **radioimmunotherapy**--...

...non-myeloablative iodine-131-labeled anti-**CD20** antibody,

therapeutic method, phase I/II trial

9/3,K,AB/5 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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11233738 BIOSIS NO.: 199800015070
Randomized controlled study of !1!3!1I-Anti-B1 versus unlabeled-anti-B1 monoclonal antibody in patients with chemotherapy **refractory** low grade non-Hodgkin's **lymphoma**.
AUTHOR: Knox Susan J(a); Goris Michael L; Davis Tom A; Trisler Kirk D(a); Saal Jeannette(a); Levy Ronald
AUTHOR ADDRESS: (a)Dep. Radiation Oncology, Stanford Univ. Hosp., Stanford, CA 94305**USA
JOURNAL: International Journal of Radiation Oncology Biology Physics 39 (2 SUPPL.):p326 **1997**
CONFERENCE/MEETING: 39th Annual Meeting of the American Society for Therapeutic Radiology and Oncology Orlando, Florida, USA October 19-23, 1997
ISSN: 0360-3016
RECORD TYPE: Citation
LANGUAGE: English
1997

...1!3!1I-Anti-B1 versus unlabeled-anti-B1 monoclonal antibody in patients with chemotherapy **refractory** low grade non-Hodgkin's **lymphoma**
.
1997
DESCRIPTORS:
...MAJOR CONCEPTS: **Radiology** (Medical Sciences)
DISEASES: chemotherapy **refractory** low grade non-Hodgkin's **lymphoma**--...

...chemotherapy-**refractory** low-grade B-cell **lymphoma**--
CHEMICALS & BIOCHEMICALS: ...murine monoclonal anti-**CD20** antibody {anti-B1...
...METHODS & EQUIPMENT: **radiotherapy**--...

...**radiologic** method, therapeutic method

9/3,K,AB/6 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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10899443 BIOSIS NO.: 199799520588
Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell **lymphoma**: A multicenter study of 106 patients.
AUTHOR: Lazzarino M(a); Orlandi E; Paulli M; Straeter J; Klersy C; Gianelli U; Gargantini L; Rousset M T; Gambacorta M; Morra E; Lavabre-Bertrand T; Magrini U; Manegold C; Bernasconi C; Moeller P
AUTHOR ADDRESS: (a)Inst. Hematol., Policlinico S. Matteo, 27100 Pavia** Italy
JOURNAL: Journal of Clinical Oncology 15 (4):p1646-1653 **1997**
ISSN: 0732-183X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: To define clinicopathologic features, response to treatment, and prognostic factors of primary mediastinal B-cell **lymphoma** (MBL), a **CD20**+ tumor recognized as a distinct entity among non-Hodgkin's lymphomas (NHL). Patients and Methods: One hundred six patients presented with disease confined to thorax (86%), bulky

mediastinum (73%), superior vena cava syndrome (47%), and contiguous infiltration (57%). Ninety-nine received doxorubicin-containing chemotherapy (CHT). Results: Thirty-five of 99 patients were primarily CHT-resistant, and 64 responded: 23 achieved complete response (CR) and 41 achieved response with residual mediastinal abnormality. Seventy-seven percent of responders received mediastinal **radiotherapy** (RT). Of 64 responders, 18 (28%) relapsed: none of 23 CR patients and 18 of 41 (44%) with residual mediastinal abnormality. Relapse-free survival rate of responders was 71% at 3 years. Actuarial 3-year survival rate was 52% for all patients and 82% for responders. Predictive factors of poor outcome were identified by logistic regression; Cox survival analysis was performed on death and relapse. Pericardial effusion (P lt .001) and Eastern Cooperative Oncology Group (ECOG) performance status gtoreq 2 (P= .009) predicted nonresponse (NR) and affected survival. Less than partial midway response to CHT predicted NR to subsequent therapies. Bulky disease was related to persistent mediastinal abnormality and risk of relapse (P = .025). Conclusion. MBL is an aggressive NHL with unique clinicopathologic aspects, often **refractory** to current CHT designed for high-grade NHL Poor performance status and pericardial effusion predict NR and poor survival. inadequate response after the first courses of front-line CHT predicts failure of subsequent treatment. Responders with bulky mediastinum or residual mediastinal abnormality after CHT are at risk of relapse. These factors should help to select high-risk patients for intensive treatments.
1997

Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell **lymphoma**: A multicenter study of 106 patients.
1997

...ABSTRACT: To define clinicopathologic features, response to treatment, and prognostic factors of primary mediastinal B-cell **lymphoma** (MBL), a **CD20**+ tumor recognized as a distinct entity among non-Hodgkin's lymphomas (NHL). Patients and Methods...

...and 41 achieved response with residual mediastinal abnormality. Seventy-seven percent of responders received mediastinal **radiotherapy** (RT). Of 64 responders, 18 (28%) relapsed: none of 23 CR patients and 18 of...

...of relapse (P = .025). Conclusion. MBL is an aggressive NHL with unique clinicopathologic aspects, often **refractory** to current CHT designed for high-grade NHL Poor performance status and pericardial effusion predict...
MISCELLANEOUS TERMS: ...NON-HODGKIN'S **LYMPHOMA**; ...

...PRIMARY MEDIASTINAL B-CELL **LYMPHOMA**;

9/3,K,AB/7 (Item 5 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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09519408 BIOSIS NO.: 199497527778
Radioimmunotherapy of **refractory** B-cell **lymphoma** with 131-I-anti-B1 (anti-**CD20**) antibody.
AUTHOR: Kaminski M S(a); Fenner M; Zasadny K R; Milik A W(a); Ross C W; Francis I R; Burgess J; Estes J; Crawford S; et al
AUTHOR ADDRESS: (a)Univ. Michigan, Ann Arbor, MI**USA
JOURNAL: Clinical Research 42 (3):p405A **1994**
CONFERENCE/MEETING: Combined Annual Meeting of the Central Society for Clinical Research, American Federation for Clinical Research, Midwest Section, Midwest Society for Pediatric Research, Society for Investigative Dermatology, Central Region, and the Midwest Society of General Internal

Medicine Chicago, Illinois, USA September 16-18, 1994
ISSN: 0009 9279
RECORD TYPE: Citation
LANGUAGE: English
1994

Radioimmunotherapy of **refractory** B-cell **lymphoma** with
131-I-anti-B1 (anti-**CD20**) antibody.
1994
...MAJOR CONCEPTS: **Radiology** (Medical Sciences

9/3,K,AB/8 (Item 6 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

09098800 BIOSIS NO.: 199497107170
Updated results of a phase I trial of 131-I-anti-B1 (anti-**CD20**)
radioimmunotherapy (RIT) for **refractory** B-cell **lymphoma**
.
AUTHOR: Kaminski M S(a); Zasadny K R; Milik A W; Ross C W; Francis I R;
Burgess J; Crawford S; et al
AUTHOR ADDRESS: (a)Univ. Mich. Med. Cent., Ann Arbor, MI**USA
JOURNAL: Blood 82 (10 SUPPL. 1):p332A **1993**
CONFERENCE/MEETING: Thirty-fifth Annual Meeting of the American Society of
Hematology St. Louis, Missouri, USA December 3-7, 1993
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1993

Updated results of a phase I trial of 131-I-anti-B1 (anti-**CD20**)
radioimmunotherapy (RIT) for **refractory** B-cell **lymphoma**
.
1993

9/3,K,AB/9 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

07205469 Genuine Article#: 136UK Number of References: 21
Title: Phase I study of the pharmacokinetics of a
radioimmunoconjugate, Y-90-T101, in patients with CD5-expressing
leukemia and **lymphoma** (ABSTRACT AVAILABLE)
Author(s): Foss FM (REPRINT) ; Raubitscheck A; Mulshine JL; Fleisher TA;
Reynolds JC; Paik CH; Neumann RD; Boland C; Perentesis P; Brown MR;
Frincke JM; Lollo CP; Larson SM; Carrasquillo JA
Corporate Source: TUFTS UNIV,NEW ENGLAND MED CTR, 750 WASHINGTON ST, NEMC
542/BOSTON//MA/02111 (REPRINT); NCI,NAVY MED ONCOL
BRANCH/BETHESDA//MD/20889; NCI,RADIAT ONCOL BRANCH/BETHESDA//MD/20889;
NIH,WARREN G MAGNUSON CLIN CTR, DEPT CLIN PATHOL/BETHESDA//MD/20892;
NIH,WARREN G MAGNUSON CLIN CTR, DEPT NUCL MED/BETHESDA//MD/20892;
HYBRITECH INC,/SAN DIEGO//CA/92121
Journal: CLINICAL CANCER RESEARCH, **1998**, V4, N11 (NOV), P2691-2700
ISSN: 1078-0432 Publication date: 19981100
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Ten patients with advanced or **refractory** CDS-expressing
hematologic neoplasms [two with chronic lymphocytic leukemia and eight
with cutaneous T-cell **lymphoma** (CTCL)] were treated in a Phase I
study with the **radioimmunoconjugate** Y-90-T101, which targets CD5+
lymphocytes, Prior imaging studies using In-111-T101 demonstrated
uptake in involved lymph nodes and skin in patients with CTCL, and

Phase I studies with unmodified T101 demonstrated transient responses. In this study, patients were treated with 5 or 10 mCi of Y-90 chelated to T101 via isothiocyanatobenzyl diethylenetriamine pentaacetic acid, along with tracer doses of In-111-T101 for imaging. The biodistribution of the **radioimmunoconjugate** was determined by measuring Y-90 and In-111 blood clearance, urine excretion, and accumulation in bone marrow and in involved skin lesions. The intravascular pharmacokinetics of Y-90 were predicted by In-111-labeled T101, The greatest differences in biodistribution between '''In and 90Y were in the higher bone accumulation of 90Y and its lower urinary excretion. Imaging studies demonstrated targeting of skin lesions and involved lymph nodes in CTCL patients. The predominant toxicity was bone marrow suppression. Rapid antigenic modulation of CD5 on circulating T and B cells was observed. Recovery of T-cell populations occurred within 2-3 weeks; however, suppression of B-cell populations persisted after 5+ weeks, All CTCL patients developed human antimouse antibody after one cycle and thus were not retreated; one patient with chronic lymphocytic leukemia received a second cycle of therapy. Partial responses occurred in five patients, two with chronic lymphocytic leukemia and three with CTCL, The median response duration was 23 weeks. One CTCL patient who subsequently received electron beam irradiation to a residual lesion is disease-free after 6 years.

Title: Phase I study of the pharmacokinetics of a **radioimmunoconjugate**, Y-90-T101, in patients with CD5-expressing leukemia and **lymphoma**
, **1998**
Abstract: Ten patients with advanced or **refractory** CDS-expressing hematologic neoplasms [two with chronic lymphocytic leukemia and eight with cutaneous T-cell **lymphoma** (CTCL)] were treated in a Phase I study with the **radioimmunoconjugate** Y-90-T101, which targets CD5+ lymphocytes, Prior imaging studies using In-111-T101 demonstrated...

...acid, along with tracer doses of In-111-T101 for imaging. The biodistribution of the **radioimmunoconjugate** was determined by measuring Y-90 and In-111 blood clearance, urine excretion, and accumulation...
...Identifiers--T-CELL **LYMPHOMA**; CHRONIC LYMPHOCYTIC-LEUKEMIA; T101 MONOCLONAL-ANTIBODY; ANTI-**CD20** ANTIBODY; **RADIOIMMUNOTHERAPY;** THERAPY; **RADIOIMMUNODETECTION;** ANTIGEN
?

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? ds

Set      Items   Description
S1      117992   REFRACTORY
S2        8434   CD20
S3         434   S1 AND S2
S4     1309423   RADIOLABEL? OR RADIO?
S5         106   S3 AND S4
S6      214151   LYMPHOMA
S7         104   S5 AND S6
S8          13   S7 AND PY<=1998
S9           9   RD (unique items)
S10         35   AU=DAVIS T AND PY=1999
S11       3802   LYMPHOMA AND CD20
S12          0   S10 AND S11
S13       8434   CD20
S14          0   S10 AND S13
S15     214151   LYMPHOMA
S16          0   S10 AND S15
S17         24   RD S10 (unique items)
S18          0   AU= DAVIS T AND JN=CLINICAL(W)CANCER(W)RESEARCH
S19        632   AU= DAVIS T
S20     218783   LYMPHOMA OR CD20
S21         20   S19 AND S20
S22         14   RD (unique items)
? s retreat?
     S23   14050  RETREAT?
? s s23 and s4
           14050  S23
         1309423  S4
     S24    1293  S23 AND S4
? s s2 and s24
            8434  S2
            1293  S24
     S25      12  S2 AND S24
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S26      11  RD (unique items)
? s s26 and py<=1998
Processing
Processing
              11  S26
        33593137  PY<=1998
     S27       2  S26 AND PY<=1998
? t s27/3,k,ab/1-2

 27/3,K,AB/1     (Item 1 from file: 34)
DIALOG(R)File  34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

07205469   Genuine Article#: 136UK   Number of References: 21
Title: Phase I study of the pharmacokinetics of a
    radioimmunoconjugate, Y-90-T101, in patients with CD5-expressing
    leukemia and lymphoma  (ABSTRACT AVAILABLE)
Author(s): Foss FM (REPRINT) ; Raubitscheck A; Mulshine JL; Fleisher TA;
    Reynolds JC; Paik CH; Neumann RD; Boland C; Perentesis P; Brown MR;
    Frincke JM; Lollo CP; Larson SM; Carrasquillo JA
Corporate Source: TUFTS UNIV,NEW ENGLAND MED CTR, 750 WASHINGTON ST, NEMC
    542/BOSTON//MA/02111 (REPRINT); NCI,NAVY MED ONCOL
    BRANCH/BETHESDA//MD/20889; NCI,RADIAT ONCOL BRANCH/BETHESDA//MD/20889;
    NIH,WARREN G MAGNUSON CLIN CTR, DEPT CLIN PATHOL/BETHESDA//MD/20892;
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NIH,WARREN G MAGNUSON CLIN CTR, DEPT NUCL MED/BETHESDA//MD/20892;
HYBRITECH INC,/SAN DIEGO//CA/92121
Journal: CLINICAL CANCER RESEARCH, **1998**, V4, N11 (NOV), P2691-2700
ISSN: 1078-0432 Publication date: 19981100
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Ten patients with advanced or refractory CDS-expressing hematologic neoplasms [two with chronic lymphocytic leukemia and eight with cutaneous T-cell lymphoma (CTCL)] were treated in a Phase I study with the **radioimmunoconjugate** Y-90-T101, which targets CD5+ lymphocytes, Prior imaging studies using In-111-T101 demonstrated uptake in involved lymph nodes and skin in patients with CTCL, and Phase I studies with unmodified T101 demonstrated transient responses. In this study, patients were treated with 5 or 10 mCi of Y-90 chelated to T101 via isothiocyanatobenzyl diethylenetriamine pentaacetic acid, along with tracer doses of In-111-T101 for imaging. The biodistribution of the **radioimmunoconjugate** was determined by measuring Y-90 and In-111 blood clearance, urine excretion, and accumulation in bone marrow and in involved skin lesions. The intravascular pharmacokinetics of Y-90 were predicted by In-111-labeled T101, The greatest differences in biodistribution between '''In and 90Y were in the higher bone accumulation of 90Y and its lower urinary excretion. Imaging studies demonstrated targeting of skin lesions and involved lymph nodes in CTCL patients. The predominant toxicity was bone marrow suppression. Rapid antigenic modulation of CD5 on circulating T and B cells was observed. Recovery of T-cell populations occurred within 2-3 weeks; however, suppression of B-cell populations persisted after 5+ weeks, All CTCL patients developed human antimouse antibody after one cycle and thus were not **retreated**; one patient with chronic lymphocytic leukemia received a second cycle of therapy. Partial responses occurred in five patients, two with chronic lymphocytic leukemia and three with CTCL, The median response duration was 23 weeks. One CTCL patient who subsequently received electron beam irradiation to a residual lesion is disease-free after 6 years.

Title: Phase I study of the pharmacokinetics of a **radioimmunoconjugate**, Y-90-T101, in patients with CD5-expressing leukemia and lymphoma
, **1998**
...Abstract: with cutaneous T-cell lymphoma (CTCL)] were treated in a Phase I study with the **radioimmunoconjugate** Y-90-T101, which targets CD5+ lymphocytes, Prior imaging studies using In-111-T101 demonstrated ...

...acid, along with tracer doses of In-111-T101 for imaging. The biodistribution of the **radioimmunoconjugate** was determined by measuring Y-90 and In-111 blood clearance, urine excretion, and accumulation...

...weeks, All CTCL patients developed human antimouse antibody after one cycle and thus were not **retreated**; one patient with chronic lymphocytic leukemia received a second cycle of therapy. Partial responses occurred...
...Identifiers--T-CELL LYMPHOMA; CHRONIC LYMPHOCYTIC-LEUKEMIA; T101 MONOCLONAL-ANTIBODY; ANTI-**CD20** ANTIBODY; **RADIOIMMUNOTHERAPY;** THERAPY; **RADIOIMMUNODETECTION;** ANTIGEN

27/3,K,AB/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

04644221 Genuine Article#: TY620 Number of References: 48
Title: YTTRIUM-90-LABELED ANTI-**CD20** MONOCLONAL-ANTIBODY THERAPY OF

RECURRENT B-CELL LYMPHOMA (Abstract Available)
Author(s): KNOX SJ; GORIS ML; TRISLER K; NEGRIN R; DAVIS T; LILES TM; GRILLOLOPEZ A; CHINN P; VARNS C; NING SC; FOWLER S; DEB N; BECKER M; MARQUEZ C; LEVY R
Corporate Source: STANFORD UNIV,MED CTR,DEPT RADIAT ONCOL A093/STANFORD//CA/94305; STANFORD UNIV,SCH MED,DEPT RADIAT ONCOL/STANFORD//CA/94305; STANFORD UNIV,SCH MED,DEPT DIAGNOST RADIOL,DIV NUCL MED/STANFORD//CA/94305; STANFORD UNIV,SCH MED,DEPT MED,DIV BONE MARROW TRANSPLANTAT/STANFORD//CA/94305; STANFORD UNIV,SCH MED,DEPT INTERNAL MED,DIV MEDONCOL/STANFORD//CA/94305; IDEC PHARMACEUT CORP/SAN DIEGO//CA/92121
Journal: CLINICAL CANCER RESEARCH, **1996**, V2, N3 (MAR), P457-470
ISSN: 1078-0432
Language: ENGLISH Document Type: ARTICLE
Abstract: A Phase I/II dose escalation study of Y-90-murine anti-**CD20** monoclonal antibody (mAb) in patients with recurrent B-cell lymphoma was performed. The primary objectives of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-**CD20** mAb on the biodistribution of In-111-anti-**CD20** mAb; (b) to determine the maximal tolerated dose of Y-90-anti-**CD20** mAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of Y-90-anti-**CD20** mAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's lymphoma were treated. Biodistribution studies with In-111-anti-**CD20** mAb were performed prior to therapy. Groups of three or four patients were treated at dose levels of similar to 13.5, 20, 30, 40, and 50 mCi Y-90-anti-**CD20** mAb. Three patients were **retreated** at the 40-mCi dose level. The use of unlabeled antibody affected the biodistribution favorably. Nonhematological toxicity was minimal. The only significant toxicity was myelosuppression. The overall response rate following a single dose of Y-90-anti-**CD20** mAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ months following treatment. **Radioimmunotherapy** with less than or equal to 50 mCi Y-90-anti-**CD20** mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of less than or equal to 40 mCi Y-90-anti-**CD20** mAb were not myeloablative.

Title: YTTRIUM-90-LABELED ANTI-**CD20** MONOCLONAL-ANTIBODY THERAPY OF RECURRENT B-CELL LYMPHOMA
, **1996**
Abstract: A Phase I/II dose escalation study of Y-90-murine anti-**CD20** monoclonal antibody (mAb) in patients with recurrent B-cell lymphoma was performed. The primary objectives of the study were: (a) to determine the effect of the preinfusion of unlabeled anti-**CD20** mAb on the biodistribution of In-111-anti-**CD20** mAb; (b) to determine the maximal tolerated dose of Y-90-anti-**CD20** mAb that does not require bone marrow transplantation; and (c) to evaluate the safety and antitumor effect of Y-90-anti-**CD20** mAb in patients with recurrent B-cell lymphoma. Eighteen patients with relapsed low- or intermediate-grade non-Hodgkin's lymphoma were treated. Biodistribution studies with In-111-anti-**CD20** mAb were performed prior to therapy. Groups of three or four patients were treated at...

...levels of similar to 13.5, 20, 30, 40, and 50 mCi Y-90-anti-**CD20** mAb. Three patients were **retreated** at the 40-mCi dose level. The use of unlabeled antibody affected the biodistribution favorably...

...toxicity was myelosuppression. The overall response rate following a single dose of Y-90-anti-**CD20** mAb therapy was 72%, with six complete responses and seven partial responses and freedom from progression of 3-29+ months following treatment. **Radioimmunotherapy** with less than or equal to 50 mCi Y-90-anti-

CD20 mAb resulted in minimal nonhematological toxicity and durable clinical responses in patients with recurrent B-cell lymphoma. Doses of less than or equal to 40 mCi Y-90-anti-**CD20** mAb were not myeloablative.

...Identifiers--NON-HODGKINS-LYMPHOMA; DOSE FRACTIONATION; **RADIOIMMUNOTHERAPY;** DOSIMETRY; TRIAL; CARCINOMA

?

c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 2805415 IFI Acc No: 9701602
Document Type: C
RADIOIMMUNOTHERAPY OF LYMPHOMA USING ANTI-**CD20**; USING **ANTIBODIES** DIRECTED TO AN ANTIGEN AND RADIOACTIVE LABELS
Inventors: Butchko Gregory M (US); Glenn Stephan D (US); Kaminski Mark S (US); Wahl Richard L (US)
Assignee: Coulter Pharmaceutical Inc
Assignee Code: 40767 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 5595721 **19970121** US 93121582 19930916
Publication Kind: A
Calculated Expiration: 20140121
(Cited in 005 later patents) Document Type: CERTIFICATE OF CORRECTION
Certificate of Correction Date: 19970701, 19971118
Priority Applic(No,Date): US 93121582 19930916

Abstract: Methods for the treatment of lymphoma by adminstration of a B cell-specific **antibody** are described. The invention encompasses providing to a patient both unlabeled **antibodies** and **antibodies** labeled with a radioisotope. A principal advantage of the method is that tumor responses can be obtained in a radiometric dose range that does not require hematopoietic stem cell replacement as an adjunct therapy.

RADIOIMMUNOTHERAPY OF LYMPHOMA USING ANTI-**CD20**; ...

...USING **ANTIBODIES** DIRECTED TO AN ANTIGEN AND RADIOACTIVE LABELS
Publication (No,Date), Applic (No,Date):
...**19970121**

Abstract: Methods for the treatment of lymphoma by adminstration of a B cell-specific **antibody** are described. The invention encompasses providing to a patient both unlabeled **antibodies** and **antibodies** labeled with a radioisotope. A principal advantage of the method is that tumor responses can...

Exemplary Claim: ...cell lymphoma, which comprises: (i) administering to a patient an imaging effective amount of an **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, trace labelled with a first radiolabel, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma; (ii) imaging the distribution of said labelled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody** or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount effective for blocking non-tumor binding sites for an **antibody**, or Fab, Fab' or F(ab')2 portion thereof effective for treating B-cell lymphoma...

...administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), this is...

...into the patient in order for the to recover hematopoietic function after administration of said **antibody** or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...
Non-exemplary Claims: 2. The method of claim 1, wherein said **antibody** is labelled with a Beta -emitter...

...3. The method of claim 2, wherein said **antibody** is labelled with

an isotope selected from the group consisting of 131I, 90Y and 186Re...

...5. The method of claim 4, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...6. The method of claim 4, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv), are labeled with 131I...

...8. The method of claim 1, wherein the **antibody** administered in step (i) is labelled with 99Tc or 111In and wherein the **antibody** administered in step (iv) is labelled with an isotope selected from the group consisting of...

...9. The method of claim 8, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...11. The method of claim 1, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...12. The method of claim 11, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof in step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof in steps (iii) and (iv), are labeled...

...13. The method of claim 1, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv) are labeled with 131I **antibody**, or a Fab, Fab' or F(ab)2, portion thereof, which binds to **CD20** antigen present on the surface of cells of B lineage that is trace-labelled with a first radiolabel; (ii) imaging the distribution of said labelled **antibody**, or Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, said amount being effective for blocking non-specific binding sites for an **antibody** effective for treating said neoplasm of B-cell lineage within the body of the patient...

...patient a radioimmunotherapeutically effective amount for treating said neoplasm of B-cell lineage of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), which binds to **CD20** antigen present on the surface of said cells of B lineage, that is labelled with ...

...the patient in order for the patient to recover hematopoietic function after administration of said **antibody**, or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...

...15. The method of claim 14, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in each of steps...

...cell lymphoma, which comprises: (i) administering to a patient an imaging effective amount of an **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma that is trace labelled with a radiolabel; (ii) imaging the distribution of said labelled **antibody**, or Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount

being effective for blocking non-tumor binding sites for an **antibody** effective for treating B-cell lymphoma within the body of the patient; and (iv) administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said labelled **antibody**, or a Fab, Fab' or F(ab)2 portion thereof of step (i), which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, wherein the amount...

...the patient to recover hematopoietic function after administration of the radioimmunotherapeutically effective amount of said **antibody**, or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically...

...17. The method of claim 16, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in each of steps...

...B-cell lymphoma, which comprises: (i) administering to a patient an effective amount of unlabeled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount effective for blocking non-tumor binding sites for said **antibody** in the body of said patient; (ii) administering an imaging effective amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i),

? ds

Set	Items	Description
S1	104	CD(W)20 OR CD20
S2	22515	ANTIBOD?
S3	93	S1 AND S2
S4	10	RITUXIMAB
S5	4	S3 AND S4

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? s s3 and py<=1998
              93  S3
         3120930  PY<=1998
      S6      23  S3 AND PY<=1998
? s s6 and py<1998
              23  S6
         2951074  PY<1998
      S7      16  S6 AND PY<1998
? t s7/3,k,ab/1-10

 7/3,K,AB/1
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 3579490  IFI Acc No: 0136239
Document Type: C
PHARMACEUTICAL COMPOSITIONS FOR IMMUNOTHERAPY CONTAINING ANTIBODIES
WHICH SPECIFICALLY RECOGNIZE THE MHCII ANTIGEN OF A PATIENT TO BE TREATED;
TREATING  RESIDUAL TUMOR CELLS, TRANSPLANTING BONE MARROW CELLS
Inventors: Lindhofer Horst (DE); Thierfelder Stefan (DE)
Assignee: GSF-Forschungszentrum fur Umwelt und Gesundheit GmbH DE
Assignee Code: 40370
Publication (No,Date), Applic (No,Date):
Publication (Kind,No,Date), Applic (No,Date):
US 6294167     20010925 US 9829369    19981123
Calculated Expiration: 20160823
PCT Pub(No,Date),Applic(No,Date): WO 977819       19970306  WO
96EP3733    19960823
    Section 371:  19981123
    Section 102(e):19981123
Priority Applic(No,Date): DE 19531346    19950825

Abstract: The invention concerns medicaments containing antibodies
which have at least one specificity and detect the MHCII antigen of a
patient to be treated. The invention further concerns antibodies with
two or more specificities which detect the MHCII antigen of a patient, and
diagnostic compositions containing these antibodies.


PHARMACEUTICAL COMPOSITIONS FOR IMMUNOTHERAPY CONTAINING ANTIBODIES
WHICH SPECIFICALLY RECOGNIZE THE MHCII ANTIGEN OF A PATIENT TO BE TREATED
...
...PCT Pub(No,Date),Applic(No,Date): 19970306

Abstract: The invention concerns medicaments containing antibodies
which have at least one specificity and detect the MHCII antigen of a
patient to be treated. The invention further concerns antibodies with
two or more specificities which detect the MHCII antigen of a patient, and
diagnostic compositions containing these antibodies.

Exemplary Claim: ...cells; and administering to said subject a
   pharmaceutically effective amount of a composition comprising an
   antibody which selectively binds to MHCII antigen expressed by
   said tumor cells, whereby as a result of said selective binding, tumor
   cells carrying an antibody-MHCII antigen complex are destroyed.
Non-exemplary Claims: 2. The method of claim 1, wherein said antibody
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is a monospecific **antibody**.
...

...3. The method of claim 1, wherein said **antibody** possesses one or more additional non-MHCII specificities...

...4. The method of claim 1, wherein said **antibody** has an additional specificity which recognizes an antigen on an effector cell...
...7. The method of claim 1, wherein said **antibody** further possesses a specificity for binding to a second antigen expressed on a cell type ...

...of CD1, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD10, CD11, CD11b, CD13, CD14, CD19, **CD20**, CD21, CD22, CD23, CD24, CD30, CD33, CD37, CD40, CD41, CD44v3, CD44v6, CD45R, CD56, CD71, B220...

...9. The method of claim 1, wherein said **antibody** is selected from the group consisting of monoclonal, recombinant, semisynthetic, chemically modified **antibodies**, and antigen binding fragments thereof...

...10. The method of claim 10, wherein said **antibody** is coupled to a moiety selected from the group consisting of an enzyme, a toxic

7/3,K,AB/2
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 3157375 IFI Acc No: 9918109
Document Type: C
CELL SURFACE PROTEIN AND EFFECTOR CELL BONDING REAGENT; NEWCASTLE DISEASE VIRUS
Inventors: Breitling Frank (DE); Dubel Stefan (DE); Gotter Stefanie (DE); Haas Claudia (DE); Khazaie Khashayarsha (DE); Kipriyanov Sergey (DE); Little Melvyn (DE); Moldenhauer Gerd (DE); Rode Hans-Jurgen (DE); Volker Schirrmacher (DE)
Assignee: Deutsches Krebsforschungszentrum DE
Assignee Code: 06121
Publication (No,Date), Applic (No,Date):
Publication (Kind,No,Date), Applic (No,Date):
US 5911987 19990615 US 97702712 19970221
Publication Kind: A
Calculated Expiration: 20160615
PCT Pub(No,Date),Applic(No,Date): WO 9524490 **19950914** WO 95EP843 19950307
Section 371: 19970221
Section 102(e):19970221
Priority Applic(No,Date): DE 4407538 19940307
Abstract: The present invention relates to a bonding reagent, which is characterized in that it comprises a first bonding component specific for the hemagglutinin-neuraminidase molecule of a Newcastle Disease Virus and a second bonding component specific for a costimulatorily acting molecule of an effector cell. Furthermore, this invention concerns a process for the production of the bonding reagent as well as a vaccine containing the bonding reagent and inactivated tumor cells.

...PCT Pub(No,Date),Applic(No,Date): **19950914**

Exemplary Claim: ...binding to the hemagglutirnin-neuraminidase molecule of a Newcastle Disease Virus or binding to an **antibody** directed against hapten 2-phenyloxazole-5-one, and a second bonding component binding to a...

Non-exemplary Claims: 2. The bonding reagent of claim 1, wherein said first bonding component is an **antibody** or a portion thereof which has a bonding domain...

...3. The bonding reagent of claim 2, wherein said portion of the **antibody** is a Fab', (Fab') sub 2, F sub V or (F sub V) sub 2...

...4. The bonding reagent of claim 1, wherein said second bonding component is an **antibody** or a portion thereof which has a bonding domain...

...5. The bonding reagent of claim 4, wherein said portion of the **antibody** is a Fab', (Fab') sub 2, F sub V or (F sub V) sub 2...

...wherein said costimulatorily acting molecule is selected from the group consisting of CD2, CD3, CD19, **CD20**, CD22, CD26, CD28, CTLA-4 receptor and MHSA...

...18. The vaccine of claim 14, wherein said cell surface protein is an **antibody**.
...

...19. The vaccine of claim 18, wherein said **antibody** is directed against hapten 2-phenyloxazole-5-one

7/3,K,AB/3
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 2913778 IFI Acc No: 9735086
Document Type: C
RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY; NUCLEIC ACID SEQUENCE ENCODING OLD WORLD MONKEY IMMUNOGLOBULIN-BINDING REGION AND SECOND SEQUENCE ENCODING HUMAN OR CHIMPANZEE REGION
Inventors: Hanna Nabil (US); Newman Roland A (US); Raab Ronald W (US)
Assignee: IDEC Pharmaceuticals Corp
Assignee Code: 40498
Publication (No,Date), Applic (No,Date):
US 5693780 **19971202** US 95481869 19950607
Publication Kind: A
Calculated Expiration: 20141202
Continuation Pub(No),Applic(No,Date): ABANDONED US 92912292 19920710
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 91735064 19910725; ABANDONED US 92856281 19920323
Division Pub(No),Applic(No,Date): US 95379072 19950125
Priority Applic(No,Date): US 95481869 19950607; US 92912292 19920710; US 91735064 19910725; US 92856281 19920323; US 95379072 19950125
Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY...
Publication (No,Date), Applic (No,Date):
...**19971202**

Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

Exemplary Claim: D R A W I N G

1. Nucleic acid encoding a recombinant **antibody** which comprises (i) a first nucleic acid sequence encoding an Old World monkey immunoglobulin antigen...

Non-exemplary Claims: 2. The nucleic acid of claim 1 wherein said recombinant **antibody** comprises a framework region selected from the group consisting of a human immunoglobulin framework region...

...8. The nucleic acid of claim 7, wherein the recombinant **antibody** contains at least one human constant region...

...10. The nucleic acid of claim 1, wherein the recombinant **antibody** comprises a human constant region...

...12. The nucleic acid of claim 10, wherein said recombinant **antibody** specifically binds to a human antigen...

...13. The nucleic acid of claim 10, wherein said **antibody** binds specifically to an antigen selected from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human ...

...14. The nucleic acid of claim 1, wherein said recombinant **antibody** specifically binds to a human antigen...

...15. The nucleic acid of claim 1 wherein said **antibody** binds specifically to an antigen selected from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human ...

7/3,K,AB/4
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 2900124 IFI Acc No: 9730811
Document Type: C
RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY; GENETIC ENGINEERING
Inventors: Hanna Nabil (US); Newman Roland A (US); Raab Ronald W (US)
Assignee: IDEC Pharmaceuticals Corp
Assignee Code: 40498
Publication (No,Date), Applic (No,Date):
US 5681722 **19971028** US 95478039 19950607
Publication Kind: A
Calculated Expiration: 20141028
Continuation Pub(No),Applic(No,Date): ABANDONED US 92912292 19920710
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 91735064 19910725; ABANDONED US 92856281 19920323
Division Pub(No),Applic(No,Date): US 95379072 19950125
Priority Applic(No,Date): US 95478039 19950607; US 92912292 19920710; US 91735064 19910725; US 92856281 19920323; US 95379072 19950125

Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY...
Publication (No,Date), Applic (No,Date):

...**19971028**

Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

Exemplary Claim: D R A W I N G

1. A method for producing a chimeric **antibody** comprising the variable region of an Old World monkey **antibody** gene and the human constant region from a human **antibody** gene, which method comprises the steps of: contacting nucleic acid from the Old World monkey...

...to the nucleic acid sequence encoding a 5' leader sequence or its complement of said **antibody** gene, to form a hybrid complex; amplifying said nucleic acid in said hybrid complex to produce amplified nucleic acid; isolating the variable region of said Old World monkey **antibody** gene, and fusing said variable region sequence to a human constant region sequence.

Non-exemplary Claims: ...4. A method for isolating the variable region of an Old World monkey **antibody** gene, comprising the steps of: contacting RNA from an Old World monkey with reverse transcriptase...

...complementary to the said cDNA at a region encoding a 5' leader sequence of said **antibody** gene, to form a hybrid complex, amplifying said nucleic acid in said hybrid complex to...

...and isolating the nucleic acid sequence encoding the variable region of said Old World monkey **antibody** gene...

...5. The method of claim 1, wherein said Old World monkey **antibody** specifically binds to a human antigen...

...from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8., human...

...from the group consisting of CD58, VCAM, VLA4, CD2, LFA3,ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human...

7/3,K,AB/5
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 2879360 IFI Acc No: 9724697
Document Type: C
ANIMAL MODEL OF THE HUMAN IMMUNE SYSTEM; MOUSE
Inventors: Gallinger Steven (CA); Hozumi Nobumichi (CA); Roder John C (CA); Sandhu Jasbir S (CA); Shpitz Baruch (IL)
Assignee: Mount Sinai Hospital Corp CA
Assignee Code: 21289
Publication (No,Date), Applic (No,Date):
US 5663481 **19970902** US 93102905 19930806
Publication Kind: A
Calculated Expiration: 20140902
Priority Applic(No,Date): US 93102905 19930806

Abstract: The present invention relates to a non-human chimeric mammal having characteristics of a functional human immune system and having functional human lymphocytes reconstituted in the mammal's lymphopoietic tissue, particularly the spleen. The invention also relates to a method of

preparing a non-human chimeric mammal, having characteristics of a functional human immune system, by engraftment of human peripheral blood leukocytes into an immunocompromised mammal. Use of the chimeric mammal as a model of the human immune system is described.

Publication (No,Date), Applic (No,Date):
...**19970902**
Non-exemplary Claims: ...in claim 1 wherein the spleen comprises 25 to 75% CD3+ cells, 10 to 25% **CD20**+ cells, 5 to 15% CD16/56+ cells, 35 to 60% TcRab+cells and 1 to...

...the human primary humoral immune response comprises the production of specific human IgM and IgG **antibodies** in response to immunization of the chimeric mouse with an antigen...

...human peripheral blood leukocytes into an immunocompromised SCID mouse, pretreated with irradiation and with an **antibody** directed to the mouse's natural killer cells, having at least 70% reconstitution of functional...

...9. A chimeric SCID mouse as claimed in claim 5 wherein the **antibody** is anti-ASGM1...

7/3,K,AB/6
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 2878930 IFI Acc No: 9724267
Document Type: C
SEPARATION APPARATUS AND METHOD; CENTRIFUGING DEVICE WITH CLOSURE, CONSTRICTION AND CHANNELS FOR CELL SEPARATION
Inventors: Vlasselaer Peter Van (US)
Assignee: Activated Cell Therapy Inc
Assignee Code: 37594 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 5663051 **19970902** US 95570397 19951211
Publication Kind: A
Calculated Expiration: 20140831
(Cited in 002 later patents)
Cont.-in-part Pub(No),Applic(No,Date): US 94299465 19940831; US 94299467 19940831; US 94299468 19940831; US 5474687 US 94299469 19940831
Priority Applic(No,Date): US 95570397 19951211; US 94299465 19940831; US 94299467 19940831; US 94299468 19940831; US 94299469 19940831

Abstract: Disclosed is an apparatus designed to be used for enriching specific cell types from cell mixtures. The apparatus includes a centrifugable device that includes a constriction defining a lower region and a defined cell separation medium. The constriction prevents mixing between the upper and lower portions of the device. Also disclosed are methods that use precisely defined cell separation media to isolate specific cells from cell mixtures, including CD34+ hematopoietic progenitor cells from blood or bone marrow, nucleated fetal cells from maternal blood, specific tumor cells, dendritic cells, natural killer cells, and natural suppressor cells from various body fluids, and for enrichment or depletion of T cell lymphocytes. Also disclosed is a density adjusted cell separation technique used to augment the above apparatus and enrichment methods. The apparatus and enrichment methods are useful in various diagnostic and therapeutic regimens.

Publication (No,Date), Applic (No,Date):
...**19970902**
Non-exemplary Claims: ...antigen is selected from the group consisting of CD-9, CD-10, CD-19 and **CD-20**.
...

...selected from the group consisting of anti-CD3, anti-CD4 and anti-CD8 mouse monoclonal **antibodies** and the specific density of the cell separation medium is 1.0605 + OR - 0.0005

7/3,K,AB/7
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 2873822 IFI Acc No: 9722647
Document Type: C
RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY; INCLUDES AN OLD WORLD MONKEY PORTION AND A HUMAN PORTION, NUCLEIC ACID ENCODING SUCH **ANTIBODIES**
Inventors: Hanna Nabil (US); Newman Roland A (US); Raab Ronald W (US)
Assignee: IDEC Pharmaceuticals Corp
Assignee Code: 40498
Publication (No,Date), Applic (No,Date):
US 5658570 **19970819** US 95379072 19950125
Publication Kind: A
Calculated Expiration: 20140819
(Cited in 002 later patents)
Continuation Pub(No),Applic(No,Date): ABANDONED US 92912292 19920710
Cont.-in-part Pub(No),Applic(No,Date): ABANDONED US 91735064 19910725; ABANDONED US 92856281 19920323
Priority Applic(No,Date): US 95379072 19950125; US 92912292 19920710; US 91735064 19910725; US 92856281 19920323

Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

RECOMBINANT **ANTIBODIES** FOR HUMAN THERAPY...

...INCLUDES AN OLD WORLD MONKEY PORTION AND A HUMAN PORTION, NUCLEIC ACID ENCODING SUCH **ANTIBODIES**
Publication (No,Date), Applic (No,Date):
...**19970819**

Abstract: Chimeric **antibodies** including an Old World monkey portion and a human portion, nucleic acid encoding such **antibodies**, Old World monkey monoclonal **antibodies**, and methods for their production and use.

Exemplary Claim: D R A W I N G

1. A chimeric **antibody** comprising an immunoglobulin constant region and an antigen binding region, said immunoglobulin constant region being...
Non-exemplary Claims: 2. A chimeric **antibody** conprising an immunoglobin variable region specific for a particular known antigen, said **antibody** comprising: (i) a constant region selected from the group consisting of human **antibody** constant region and chimpanzee **antibody** constant region; (ii) a framework region selected from the group consisting of human **antibody** framework region,

chimpanzee **antibody** framework region and first Old World monkey **antibody** framework region; and (iii) a second Old World monkey **antibody** antigen binding portion...

...3. The **antibody** of claim 1 or 2 wherein said **antibody** binds specifically to a human antigen...

...4. The **antibody** of claim 1 or 2 wherein one said Old World monkey is a cynomolgus monkey...

...5. The **antibody** of claim 1, wherein said **antibody** binds specifically to a human antigen...

...6. The **antibody** of claim 1 or 2 wherein said **antibody** binds specifically to human antigens selected from the group consisting of CD58, VCAM, VDA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human...

...7. The **antibody** of claim 3 wherein said **antibody** binds specifically to human antigens selected from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human...

...8. The **antibody** of claim 4 wherein said **antibody** binds specifically to human antigens selected from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD23, CD25, CD4, CD19, **CD20**, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human T...

...9. The **antibody** of claim 1 wherein each said Old World monkey is selected from the group consisting...

...10. The **antibody** of claim 1 or 2 wherein said antigen-binding region comprises complementarity determining regions of...

...11. The **antibody** of claim 1 or 2 wherein said antigen-binding portion comprises the whole variable region...

...12. A method for producing a recombinant **antibody** to a human antigen, said **antibody** being not immunogenic in a human, comprising the steps of: a) raising an Old World monkey **antibody** to said antigen in an Old World monkey, b) isolating an Old World monkey nucleic acid encoding an antigen-binding region of a variable region of said Old World monkey **antibody**, c) providing a human nucleic acid encoding a human constant region of a human **antibody**, d) ligating said Old World monkey nucleic acid and said human nucleic acid ...a recombinant nucleic acid, and e) expressing said recombinant nucleic acid to produce said recombinant **antibody**.

...

...further comprises the step of immortalizing a cell able to produce said Old World monkey **antibody**.

...

...16. The method of claim 12, further comprising the step of ascertaining whether said recombinant **antibody** binds to said human antigen...

...20. The method of claim 15 wherein said recombinant **antibody** is produced in a library which is capable of expressing recombinant immunoglobulins...

...cell from said Old World monkey wherein said B-cell expresses said Old

World Monkey **antibody**.
...

...comprises screening cells of said Old World monkey for production of said Old World Monkey **antibody**.
...from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human...

...28. A recombinant **antibody** comprising (1) a constant region of a heavy chain of a human **antibody**; (2) a constant region of a light chain of said human **antibody**; (3) a variable region of a heavy chain of an Old World monkey **antibody** specific for a human antigen; and (4) a variable region of a light chain of said Old World monkey **antibody**.
...

...29. A composition comprising an **antibody** of any of claims 1 or 2 in an acceptable carrier...

...30. The composition of claim 29 where said **antibody** binds specifically to CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, **CD20**, CD23, CD41, CD44, CD54, TNF Alpha , TNF Beta , Tn antigen, IL-1, IL-8, human...

...31. The **antibody** of claim 2 wherein said first Old World monkey and said second Old World monkey...

...32. The **antibody** of claim 2 wherein said first Old World monkey and said second Old World monkey...

...33. An anti-CD4 **antibody** which comprises the variable light and variable heavy regions encoded by the DNA sequences set...

...34. The **antibody** of claim 33, wherein said **antibody** is a chimeric recombinant **antibody** which contains a constant region selected from the group consisting of human constant regions and Old World monkey constant regions which is from a different Old World Monkey **antibody** that is used to obtain said variable light and variable heavy regions...
...35. The chimeric recombinant **antibody** of claim 34, wherein said human constant regions are selected from the group consisting of...

...36. The chimeric recombinant **antibody** of claim 35, wherein the **antibody** is produced by ATCC Accession No. 69030...

...37. The **antibody** of claim 2 wherein one said Old World monkey is a Rhesus monkey38. The method of claim 12 wherein said recombinant **antibody** is expressed using a vector comprising a selectable marker gene containing an altered translation initiation...

7/3,K,AB/8
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 2831845 IFI Acc No: 9709866
Document Type: C
LIPOSOMES FOR TREATMENT OF B-CELL AND T-CELL DISORDERS; ADMINISTERING A SUSPENSION OF LIPOSOMES HAVING A SURFACE COATING OF POLYETHYLENE GLYCOL CHAINS
Inventors: Allen Theresa M (CA); Martin Francis J (US)
Assignee: Sequus Pharmaceuticals Inc
Assignee Code: 39039

Publication (No,Date), Applic (No,Date):
US 5620689 **19970415** US 95475050 19950607
Publication Kind: A
Calculated Expiration: 20140415
(Cited in 028 later patents)
Cont.-in-part Pub(No),Applic(No,Date): US 5013556 US 89425224 19891010; US 5213804 US 91642321 19911115; US 5527528 US 9340544 19930331
Priority Applic(No,Date): US 95475050 19950607; US 89425224 19891010; US 91642321 19911115; US 9340544 19930331

Abstract: A method of treating a subject having a disorder characterized by a neoplasm of B-lymphocyte or T-lymphocyte lineage cells is described. The method includes administering a suspension of liposomes having a surface coating of polyethylene glycol chains. Attached to the distal ends of the chains are **antibodies** or **antibody** fragments effective to bind to an antigen specific to the affected cells. In one embodiment, anti-CD19 **antibodies** are attached to the liposome-bound chains, for treatment of multiple myeloma.

Publication (No,Date), Applic (No,Date):
...**19970415**

Abstract: ...surface coating of polyethylene glycol chains. Attached to the distal ends of the chains are **antibodies** or **antibody** fragments effective to bind to an antigen specific to the affected cells. In one embodiment, anti-CD19 **antibodies** are attached to the liposome-bound chains, for treatment of multiple myeloma.

Exemplary Claim: ...entrapped form, and covalently attached to the distal ends of a portion of said chains, **antibodies** or **antibody** fragments effective to bind to an antigen specific for said cells.
Non-exemplary Claims: ...The method of claim 1, wherein said administering includes administration of liposomes having an attached **antibody** selected from the group consisting of anti-CD19 , anti-**CD20** and anti-CD22, for binding to a B-cell antigen...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD19 **antibody**, and said disorder is multiple myeloma...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD19 **antibody**, and said disorder is acute lymphocytic leukemia...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD19 **antibody**, and said disorder is a B-cell lymphoma...

...method of claim 2, wherein said administering includes administration of liposomes having an attached anti-**CD20** **antibody**, and said disorder is multiple myeloma...

...method of claim 2, wherein said administering includes administration of liposomes having an attached anti-**CD20** **antibody**, and said disorder is acute lymphocytic leukemia...
...method of claim 2, wherein said administering includes administration of liposomes having an attached anti-**CD20** **antibody**, and said disorder is a B-cell lymphoma...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD22 **antibody**, and said disorder is multiple myeloma...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD22 **antibody**, and said disorder is acute lymphocytic leukemia...

...of claim 2, wherein said administering includes administration of liposomes having an attached anti-CD22 **antibody**, and said disorder is a B-cell lymphoma...

...The method of claim 1, wherein said administering includes administration of liposomes having an attached **antibody** selected from the group consisting of anti-CD4 and anti-CD8, for binding to a...

...of claim 13, wherein said administering includes administration of liposomes having an attached anti-CD4 **antibody**, and said disorder is a T-cell lymphoma...

...of claim 13, wherein said administering includes administration of liposomes having an attached anti-CD4 **antibody** and said disorder is acute lymphocytic leukemia...

7/3,K,AB/9
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 2805415 IFI Acc No: 9701602
Document Type: C
RADIOIMMUNOTHERAPY OF LYMPHOMA USING ANTI-**CD20**; USING **ANTIBODIES** DIRECTED TO AN ANTIGEN AND RADIOACTIVE LABELS
Inventors: Butchko Gregory M (US); Glenn Stephan D (US); Kaminski Mark S (US); Wahl Richard L (US)
Assignee: Coulter Pharmaceutical Inc
Assignee Code: 40767 Document Type: REASSIGNED
Publication (No,Date), Applic (No,Date):
US 5595721 **19970121** US 93121582 19930916
Publication Kind: A
Calculated Expiration: 20140121
(Cited in 005 later patents) Document Type: CERTIFICATE OF CORRECTION
Certificate of Correction Date: 19970701, 19971118
Priority Applic(No,Date): US 93121582 19930916

Abstract: Methods for the treatment of lymphoma by adminstration of a B cell-specific **antibody** are described. The invention encompasses providing to a patient both unlabeled **antibodies** and **antibodies** labeled with a radioisotope. A principal advantage of the method is that tumor responses can be obtained in a radiometric dose range that does not require hematopoietic stem cell replacement as an adjunct therapy.

RADIOIMMUNOTHERAPY OF LYMPHOMA USING ANTI-**CD20**; ...

...USING **ANTIBODIES** DIRECTED TO AN ANTIGEN AND RADIOACTIVE LABELS
Publication (No,Date), Applic (No,Date):
...**19970121**

Abstract: Methods for the treatment of lymphoma by adminstration of a B cell-specific **antibody** are described. The invention encompasses providing to a patient both unlabeled **antibodies** and **antibodies** labeled with a radioisotope. A principal advantage of the method is that tumor responses can...

Exemplary Claim: ...cell lymphoma, which comprises: (i) administering to a patient an imaging effective amount of an **antibody**, or a Fab, Fab'

or F(ab')2 portion thereof, trace labelled with a first radiolabel, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma; (ii) imaging the distribution of said labelled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody** or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount effective for blocking non-tumor binding sites for an **antibody**, or Fab, Fab' or F(ab')2 portion thereof effective for treating B-cell lymphoma...

...administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), this is...

...into the patient in order for the to recover hematopoietic function after administration of said **antibody** or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...

Non-exemplary Claims: 2. The method of claim 1, wherein said **antibody** is labelled with a Beta -emitter...

...3. The method of claim 2, wherein said **antibody** is labelled with an isotope selected from the group consisting of 131I, 90Y and 186Re...

...5. The method of claim 4, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...6. The method of claim 4, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv), are labeled with 131I...

...8. The method of claim 1, wherein the **antibody** administered in step (i) is labelled with 99Tc or 111In and wherein the **antibody** administered in step (iv) is labelled with an isotope selected from the group consisting of...

...9. The method of claim 8, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...11. The method of claim 1, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in steps (iii) and...

...12. The method of claim 11, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof in step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof in steps (iii) and (iv), are labeled...

...13. The method of claim 1, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (i), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv) are labeled with 131I **antibody**, or a Fab, Fab' or F(ab)2, portion thereof, which binds to **CD20** antigen present on the surface of cells of B lineage that is trace-labelled with a first radiolabel; (ii) imaging the distribution of said labelled **antibody**, or Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, said amount being effective for blocking non-specific binding sites for an **antibody** effective for treating said neoplasm of B-cell lineage within the body of the patient...

...patient a radioimmunotherapeutically effective amount for treating said

neoplasm of B-cell lineage of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), which binds to **CD20** antigen present on the surface of said cells of B lineage, that is labelled with ...

...the patient in order for the patient to recover hematopoietic function after administration of said **antibody**, or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...

...15. The method of claim 14, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in each of steps...

...cell lymphoma, which comprises: (i) administering to a patient an imaging effective amount of an **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma that is trace labelled with a radiolabel; (ii) imaging the distribution of said labelled **antibody**, or Fab, Fab' or F(ab')2 portion thereof of step (i), within the body of the patient; (iii) administering to the patient an amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i) in unlabelled form, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount being effective for blocking non-tumor binding sites for an **antibody** effective for treating B-cell lymphoma within the body of the patient; and (iv) administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said labelled **antibody**, or a Fab, Fab' or F(ab)2 portion thereof of step (i), which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, wherein the amount...

...the patient to recover hematopoietic function after administration of the radioimmunotherapeutically effective amount of said **antibody**, or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically...

...17. The method of claim 16, wherein the amount of **antibody** administered in step (i) is the same as the amount administered in each of steps...

...B-cell lymphoma, which comprises: (i) administering to a patient an effective amount of unlabeled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount effective for blocking non-tumor binding sites for said **antibody** in the body of said patient; (ii) administering an imaging effective amount of the **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, that is trace-labelled with a first radiolabel; (iii) imaging the distribution of said labelled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (ii), within the body of the patient; (iv) administering to the patient an amount of the unlabelled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said amount effective for blocking non-tumor binding sites for an **antibody** effective for treating B-cell lymphoma, or Fab, Fab' or F(ab')2 portion thereof...

...administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, of step (ii) which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, that is labelled...

...the patient in order for the patient to recover hematopoietic function after administration of said **antibody** or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...

...19. The method of claim 18, wherein the amount of **antibody** administered in step (ii) is the same as the amount administered in step (iv...

...20. The method of claim 19, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (ii), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv), are labeled with 131I...

...21. The method of claim 18, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (ii), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (v), are labeled with 131I...

...cell lymphoma, which comprises: (i) administering to a patient a first amount of an unlabeled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, said first amount effective for blocking non-tumor binding sites for said **antibody** in the body of said patient; (ii) administering to a patient an imaging effective amount of said **antibody**, or a Fab, Fab' or F(ab')2 portion thereof of step (i), which is trace-labeled with a first radiolabel; (iii) imaging the distribution of said labelled **antibody**, or Fab, Fab' or F(ab')2 portion thereof of step (ii), within the body of the patient; (iv) administering to the patient a second amount of the unlabelled **antibody**, or a Fab, Fab' or F(ab')2 portion thereof, as was used in step (i), said second amount effective for blocking non-tumor **antibody** binding sites within the body of the patient; and (v) administering to the patient a radioimmunotherapeutically effective amount for treating B-cell lymphoma of said **antibody**, or a Fab, Fab' or F(ab)2 portion thereof of step (ii), which binds to **CD20** antigen present on the surface of cells of said B-cell lymphoma, that is labelled...

...the patient in order for the patient to recover hematopoietic function after administration of said **antibody**, or Fab, Fab' or F(ab')2 portion thereof which is administered in said radioimmunotherapeutically ...

...23. The method of claim 22, wherein the amount of **antibody** administered in step (ii) is the same as the amount administered in the therapeutic step...

...24. The method of claim 23, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (ii), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (iv), are labeled with 131I...

...25. The method of claim 22, wherein the **antibody**, or Fab, Fab' or F(ab')2 fragment thereof of step (ii), and the **antibody**, Fab, Fab' or F(ab')2 fragment thereof of step (v), are labeled with 131I.

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METHOD OF KILLING B CELLS USING **ANTIBODIES** WHICH BIND CDIM; ANTITUMOR, AUTOIMMUNE
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Abstract: Methods are provided for inducing cell death in B-cells, including neoplastic B-cells, by employing reagents that bind to a B-cell epitope. Particularly, **antibodies** specific for the marker can be administered to a host to induce death in B-cells to which the **antibodies** bind or can be used in ex vivo clinical situations to selectively remove B-cells. A B-cell specific oligosaccharide epitope useful as a B-cell marker has been identified. The ligand being recognized on B lymphocytes has no apparent similarities to any of the known pan-B cells markers. In addition, proteins which specifically bind the disclosed epitope are provided. Human monoclonal **antibody** 216, which recognizes this B-cell epitope, is cytotoxic to B-cells and binds all CD19+ and **CD20**+ B lymphocytes in human peripheral blood and spleen. Furthermore, MAb 216 does not distinguish B cells by the isotype expressed, binding IgG+ and IgM+ cells with equal intensity, and also bind all B cells regardless of their CD5 expression. Methods to inhibit neoplastic B-cell growth by administering a B-cellcytotoxic protein are presented. These products and methods find use in diagnosis and therapy.

METHOD OF KILLING B CELLS USING **ANTIBODIES** WHICH BIND CDIM...
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Abstract: ...including neoplastic B-cells, by employing reagents that bind to a B-cell epitope. Particularly, **antibodies** specific for the marker can be administered to a host to induce death in B-cells to which the **antibodies** bind or can be used in ex vivo clinical situations to selectively remove B-cells...

...cells markers. In addition, proteins which specifically bind the disclosed epitope are provided. Human monoclonal **antibody** 216, which recognizes this B-cell epitope, is cytotoxic to B-cells and binds all CD19+ and **CD20**+ B lymphocytes in human peripheral blood and spleen. Furthermore, MAb 216 does not distinguish B...

Exemplary Claim: ...said method comprising: contacting said mixed population of cells with a cytotoxic amount of an **antibody** that binds a CDIM epitope and is capable of cross-linking CDIM epitopes on the...
Non-exemplary Claims: 2. A method according to claim 1, wherein said **antibody** is a monoclonal **antibody**.
...

...3. A method according to claim 2, wherein said monoclonal **antibody** is a human **antibody**.
...

...4. A method according to claim 2, wherein said monoclonal **antibody** is an IgM...

...10. A method according to claim 7, wherein said **antibody** is a monoclonal **antibody**.
...

...11. A method according to claim 10, wherein said **antibody** is a human IgM...

...having at least two CDIM epitopes, the method comprising: providing a cytotoxic amount of an **antibody** that binds the CDIM epitope and is capable of cross-linking CDIM epitopes on the surface of the B cell, and contacting the **antibody** with the B cells to effect binding of the **antibody** to the B cells, wherein the binding of the **antibody** results in the cross-linking of CDIM epitopes and the killing of the B cells...

...13. A method according to claim 12, wherein the step of contacting the **antibody** with the B cells further comprises parenterally administering the **antibody** in a physiologically acceptable carrier ...

...14. A method according to claim 12, wherein the step of contacting the **antibody** with the B cells further comprises systemically administering the **antibody** in a physiologically acceptable carrier.

?